Opioid Induced Hyperalgesia

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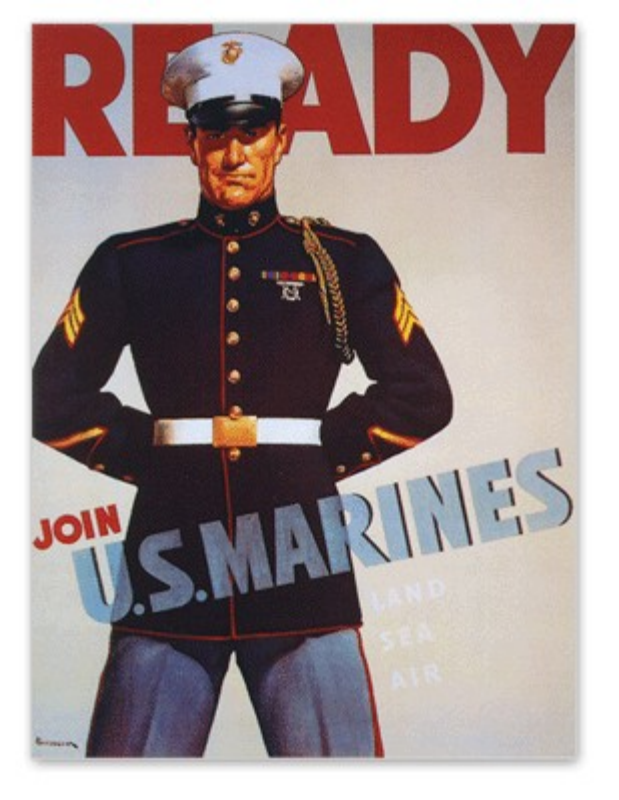
Case Presentation



- 24 y/o USMC SGT POD #1 Right BKA
- Extensive B/L LE trauma 6 months ago requiring a left BKA, and right ankle and foot fusion.
- Because the right fused foot and ankle are non functional and painful, he has elected a BKA with a prosthesis.
- “Difficult pain control” in previous admission but currently is off all pain medications.
- Underwent a diagnostic posterior tibial n. block with complete pain relief.
- Hydromorphone allergy w/anaphylaxis x2.
- No other medical problems.

Case Presentation

- GA w/ L4-5 epidural, Rec'd 10 mcg/kg fentanyl and 0.2 mg/kg morphine intraop.
- Morphine PCA 2mg q6 minutes, Ropivicaine 0.2% via epidural at 12 ml/hr.
- POD #1 10/10 pain, pt. unable to communicate. Test dose of 1% lidocaine via epidural 3 mlx2 yields complete pain relief . Epidural infusion increased to bupivicaine 0.25% at 12 ml/hr.
- 1 hour later once again in severe pain with hyperalgesia and allodynia. Almost no relief with PCA, no response to epidural bolus. Multimodal therapy with COX2, benzodiazepenes, methadone also provide no relief.
- Over the next hours, PCA rapidly escalated to ~0.1 mg/kg every 6 minutes ie 1 mg/kg/hr.
- Eventually, he is transferred to ICU, maintained on morphine PCA which he uses throughout the night to the point of non responsiveness. Vital signs remain stable.

Case Presentation

- The next morning, he is awake and alert, still with subjective pain.
- He is transferred to the ward, PCA usage decreases rapidly over the next day and he is discharged on POD #3.
- 2 weeks later is off all opioids.
- 3 months later ...

Case Presentation

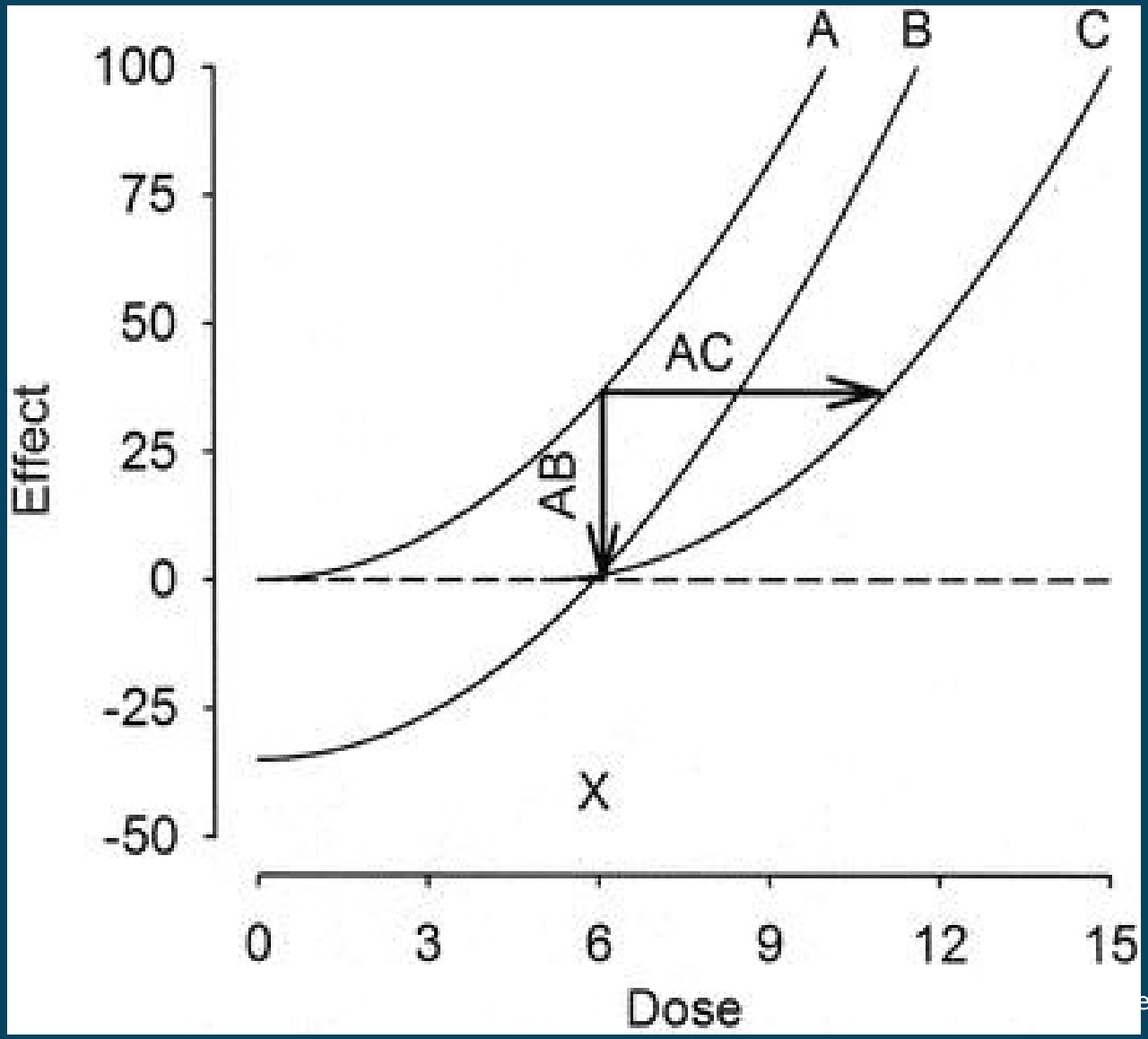
Objectives

- What is opioid induced hyperalgesia (OIH)?
  - Tolerance v. OIH
- What evidence is there that it exists?
  - Animal Studies
  - Human Studies
- Prevention/Treatment
  - Relationship between OIH and NMDA receptors.
  - Clinical uses and side effects of ketamine
- Revisit Case Presentation

Introduction

- According to the world health organization, pain is “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.
- Hyperalgesia is an increased response to a stimulus that is normally painful.
- Allodynia is pain from stimuli that are not normally painful.

What is OIH



Curve A – normal opioid responses

Curve B – Hyperalgesia

Curve C - Tolerance

esiology 2006

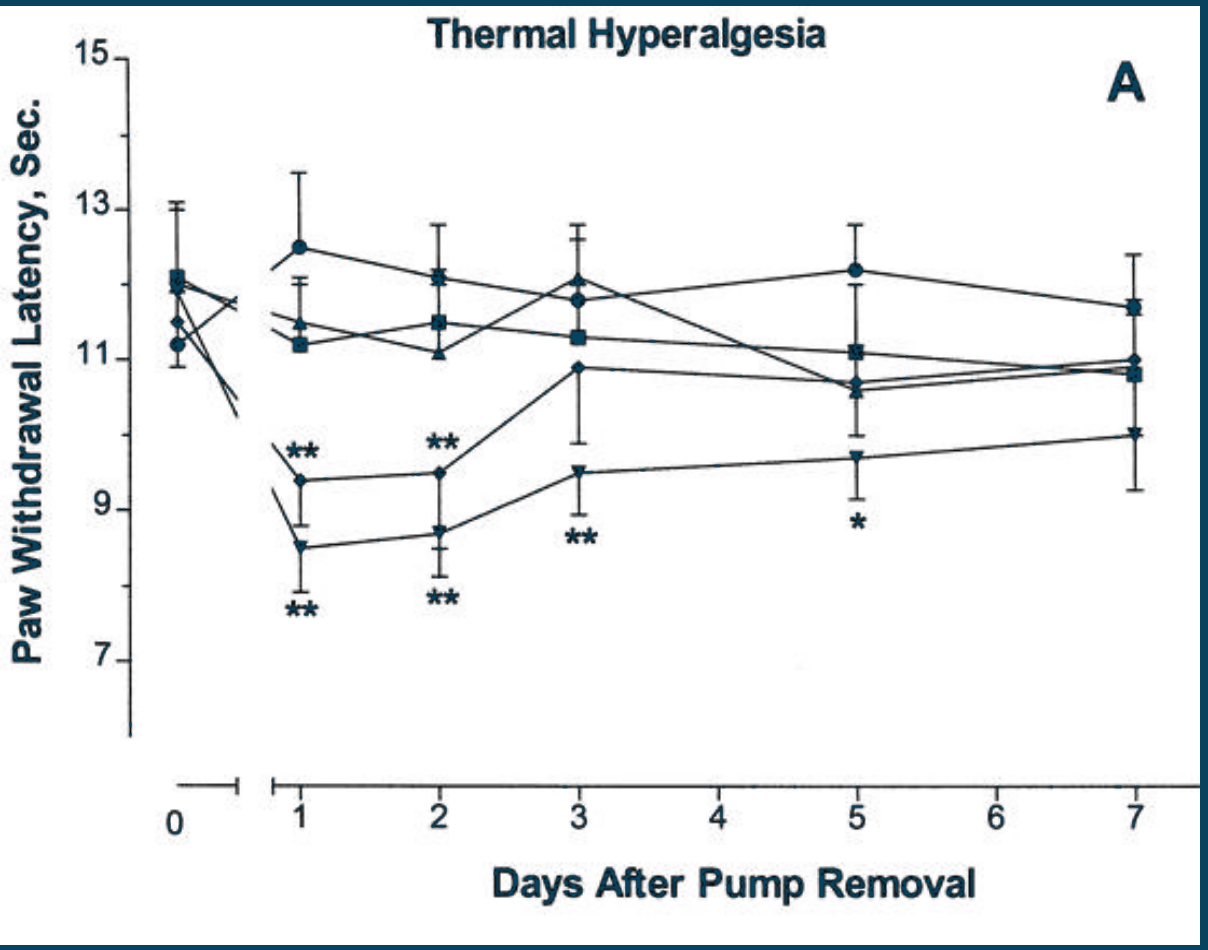
Animal Studies

Investigator(s), yr	Reference	Animal	Route	Drug	Nociceptive Test	Mechanism(s) Explored
Aley and Levine, 1995	50	Rat	ID	DAMGO	Mechanical	
Aley and Levine, 1997	51	Rat	ID	DAMGO	Mechanical	AC, calcium, PKC
Aley and Levine, 1997	52	Rat	ID	DAMGO	Mechanical	PKC
Aley and Levine, 1997	53	Rat	ID	DAMGO	Mechanical	
Arts *et al.*, 1991	54	Mouse	ICV	Morphine	Thermal	Dynorphin
Bederson *et al.*, 1990	142	Rat	IV	Morphine	Thermal	RVM (on cell/off cell activity)
Bie *et al.*, 2003	143	Rat	IV	Morphine	Thermal	NRM (α1-adrenergic receptor)
Bie, 2003	144	Rat	IP	Morphine	Thermal	NRM (κ-opioid receptor)
Burdin *et al.*, 1992	145	Rat	PAG	Morphine	Electrical	PAG (opioid modulation)
Celerier *et al.*, 1999	38	Rat	SC	Morphine Fentanyl	Mechanical	NMDA receptor
Celerier *et al.*, 2000	43	Rat	SC	Fentanyl	Mechanical	NMDA receptor
Celerier *et al.*, 2001	37	Rat	SC	Heroin	Mechanical	NMDA receptor
Celerier *et al.*, 2004	39	Mouse	SC	Fentanyl	Mechanical Chemical	PKCγ
Christensen and Kayser, 2000	146	Rat	SC	Morphine	Mechanical	
Colpaert *et al.*, 2002	147	Rat	SC	Morphine	Mechanical	
Crain and Shen, 2004	136	Rat	SC	Morphine	Thermal	Neuraminidase/GM1 ganglioside
Davies *et al.*, 2003	49	Mouse	SC	Morphine	Mechanical	
Doerr and Kristal, 1991	148	Rat	IP	Morphine	Thermal	Amniotic fluid
Dunbar and Pulai, 1998	60	Rat	IT	Morphine	Thermal	NMDA receptor
Dunbar *et al.*, 2000	65	Rat	IT	Morphine	Thermal	Cyclooxygenase
Dunbar and Karamian, 2003	100	Rat	IT	Morphine	Thermal	EAA release, NMDA receptor
Ekblom *et al.*, 1993	149	Rat	IV	Morphine	Thermal	
Galeotti *et al.*, 2002	150	Mouse	Oral	Morphine	Thermal	Caffeine, indomethacin, prochlorperazine
Gardell *et al.*, 2002	76	Rat	SC	Morphine	Mechanical Thermal	Dynorphin
Grilly *et al.*, 1981	151	Rat	SC	Morphine	Electrical	
Grilly *et al.*, 1986	152	Rat	SC	Morphine	Electrical	
Harris *et al.*, 2004	153	Rat	IP	Morphine	Thermal	
Heinzen and Pollack, 2004	154	Rat	IV	Morphine	Electrical	NOS
Hendrie, 1985	137	Rat	Oral	Morphine	Thermal	Adrenocorticotropin
Hendrie, 1989	155	Mouse	IP	Morphine	Thermal	Endogenous opioid system
Hoffmann *et al.*, 1998	156	Rat	SC	Morphine	Thermal	Genetic factors
Ibuki *et al.*, 1997	45	Rat	IT	Morphine	Thermal	NMDA receptor, EAA
Johnston *et al.*, 2004	66	Rat	IT	Morphine	Thermal	Cytokines
Kang *et al.*, 2002	157	Rat		Fentanyl	Thermal Mechanical	Cyclooxygenase activity
Kaplan and Fields, 1991	158	Rat	RVM, IV	Morphine	Thermal	RVM
Kayan and Mitchell, 1968	159	Cat	SC	Morphine	Electrical	
Kayan *et al.*, 1971	32	Rat	SC	Morphine	Thermal	
Kest *et al.*, 2002	160	Mouse	SC	Morphine	Thermal	Genetic factors
Khasar *et al.*, 1995	55	Rat	ID	DAMGO	Thermal	AC
Kim *et al.*, 1990	161	Rat	IV	Morphine	Thermal	
Kim and Siegel, 2001	162	Rat	IV	Morphine	Thermal	Cholecystokinin
Kissin *et al.*, 2000	163	Rat	IV	Alfentanil	Mechanical	NMDA receptor
Lane *et al.*, 2004	164	Rat	PAG	Morphine	Thermal	PAG
Larcher *et al.*, 1998	165	Rat	SC	Heroin	Mechanical	NMDA receptor
Laulin *et al.*, 1999	40	Rat	SC	Heroin	Mechanical	NMDA receptor
Laulin *et al.*, 2002	42	Rat	SC	Fentanyl	Mechanical	NMDA receptor
Li *et al.*, 2001	36	Rat	SC	Morphine	Thermal, mechanical, incision	Endogenous opioid system
Li *et al.*, 2001	46	Mouse	SC	Morphine Fentanyl	Thermal, mechanical, chemical	NMDA, NOS and HO receptors
Li and Clark, 2002	35	Mouse	SC	Morphine	Thermal, mechanical, IT neurotransmitters	Glutamate, substance P
Liang *et al.*, 2003	73	Mouse	SC	Morphine	Thermal, mechanical	HO system
Manning *et al.*, 1996	166	Rat	SC	Morphine	Thermal	NMDA receptor
Mao *et al.*, 1994	48	Rat	IT	Morphine	Thermal	NMDA receptor, non-NMDA glutamate receptor, PKC
Mao *et al.*, 2002	62	Rat	IT	Morphine	Thermal	Glutamate transporters, NMDA receptor
McNally and Akil, 2002	167	Rat	SC	Morphine	Thermal	Corticotropin-releasing hormone
Milne *et al.*, 1985	168	Rat	SC	Morphine	Thermal	
Ohnishi *et al.*, 1990	169	Mouse	SC	Morphine	Chemical	Calcium ion channel
Plesan *et al.*, 1999	170	Rat	SC	Morphine	Thermal	NMDA receptor
Raghavendra *et al.*, 2002	171	Rat	SC	Morphine	Thermal, mechanical	Glia/cytokines
Raghavendra *et al.*, 2003	75	Rat	SC	Morphine	Thermal, mechanical	Glia/cytokines
Raghavendra *et al.*, 2004	172	Rat	SC	Morphine	Thermal, mechanical	Glia/cytokines
Rivat *et al.*, 2002	44	Rat	SC	Fentanyl	Chemical	NMDA receptor
Salimov *et al.*, 1993	173	Mouse	SC	Morphine	Thermal	Alcohol deprivation
Schmidt and Way, 1980	174	Mouse	SC	Morphine	Thermal	Calcium
Shen and Crain, 2001	175	Mouse	SC	Morphine	Thermal	Cholera toxin
Sweitzer *et al.*, 2004	176	Mouse	SC	Morphine	Thermal, mechanical	
Sweitzer *et al.*, 2004	71	Mouse	SC	Morphine	Thermal	PKC
Tilson *et al.*, 1973	33	Rat	IP	Morphine	Electrical	
Tislon and Reech, 1974	177	Rat	SC	Morphine	Electrical	p-chlorophenylalanine
Vanderah *et al.*, 2000	64	Rat	IT	DAMGO	Thermal, mechanical	Dynorphin
Vanderah *et al.*, 2001	47	Rat	SC	Morphine	Thermal, mechanical	RVM
VonVoigtlander and Lewis, 1983	34	Mouse	SC	Morphine, pentazocine, ethylketocyclazocine, nalbuphine, butorphanol	Chemical	
Welin *et al.*, 1994	178	Rat	SC	Morphine	Mechanical	
Wilcox *et al.*, 1979	179	Rat	SC	Morphine	Electrical	
Yu *et al.*, 1997	180	Rat	IT	Morphine	Thermal, mechanical	
Zeitz *et al.*, 2001	70	Mouse	SC	Morphine	Chemical	PKC

AC = adenylate cyclase; DAMGO = Tyr-D-Ala-Gly-(me) Phe-Gly-ol; EAA = excitatory amino acids; HO = heme oxygenase; ICV = intracerebroventricular; ID = intradermal; IP = intraperitoneal; IT = intrathecal; IV = intravenous; NMDA = *N*-methyl-D-aspartate; NOS = nitric oxide synthase; NRM = nucleus raphe magnus; PAG = periaqueductal gray; PKC = phosphokinase C; RVM = rostral ventral medulla; SC = subcutaneous.

Angst – Anesthesiology 2006.

Animal Studies



Squares - Control

Triangles - Naloxone

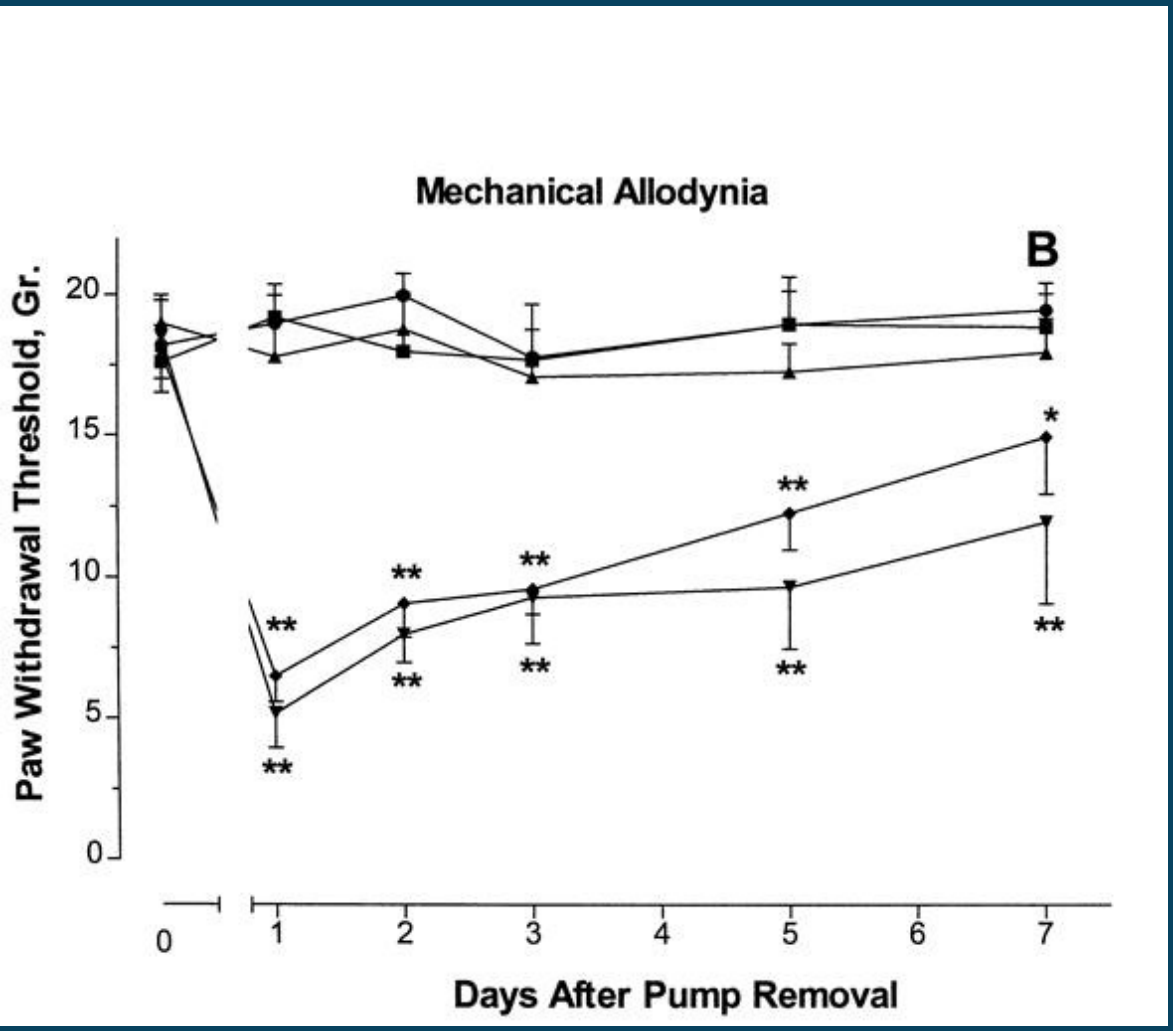
Diamonds –Morphine

Triangles Down - Morphine, intermittent naloxone

Circles - Morphine, continuous naloxone

Li, Angst. Anesth Analg 2001.

Animal Studies



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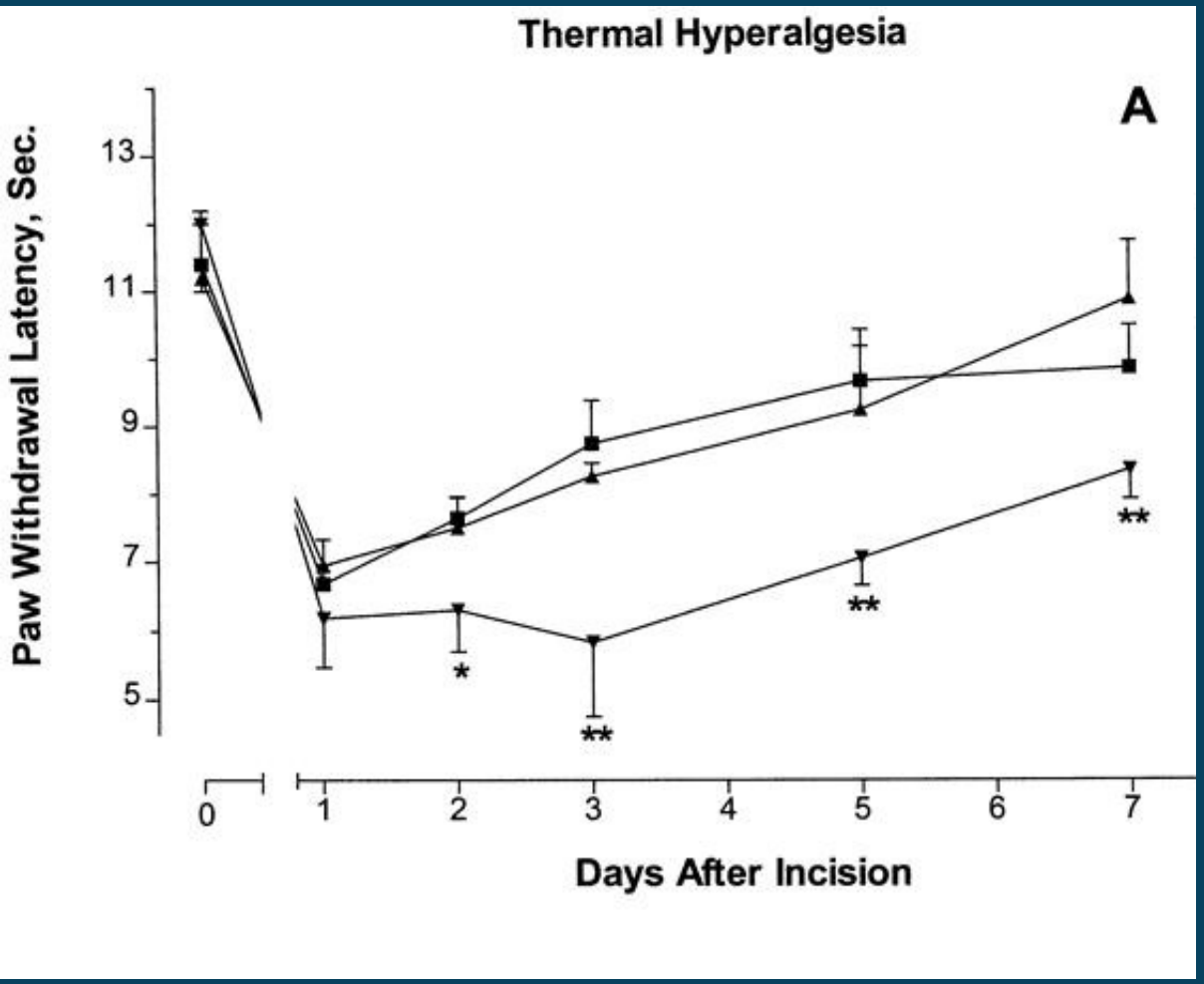


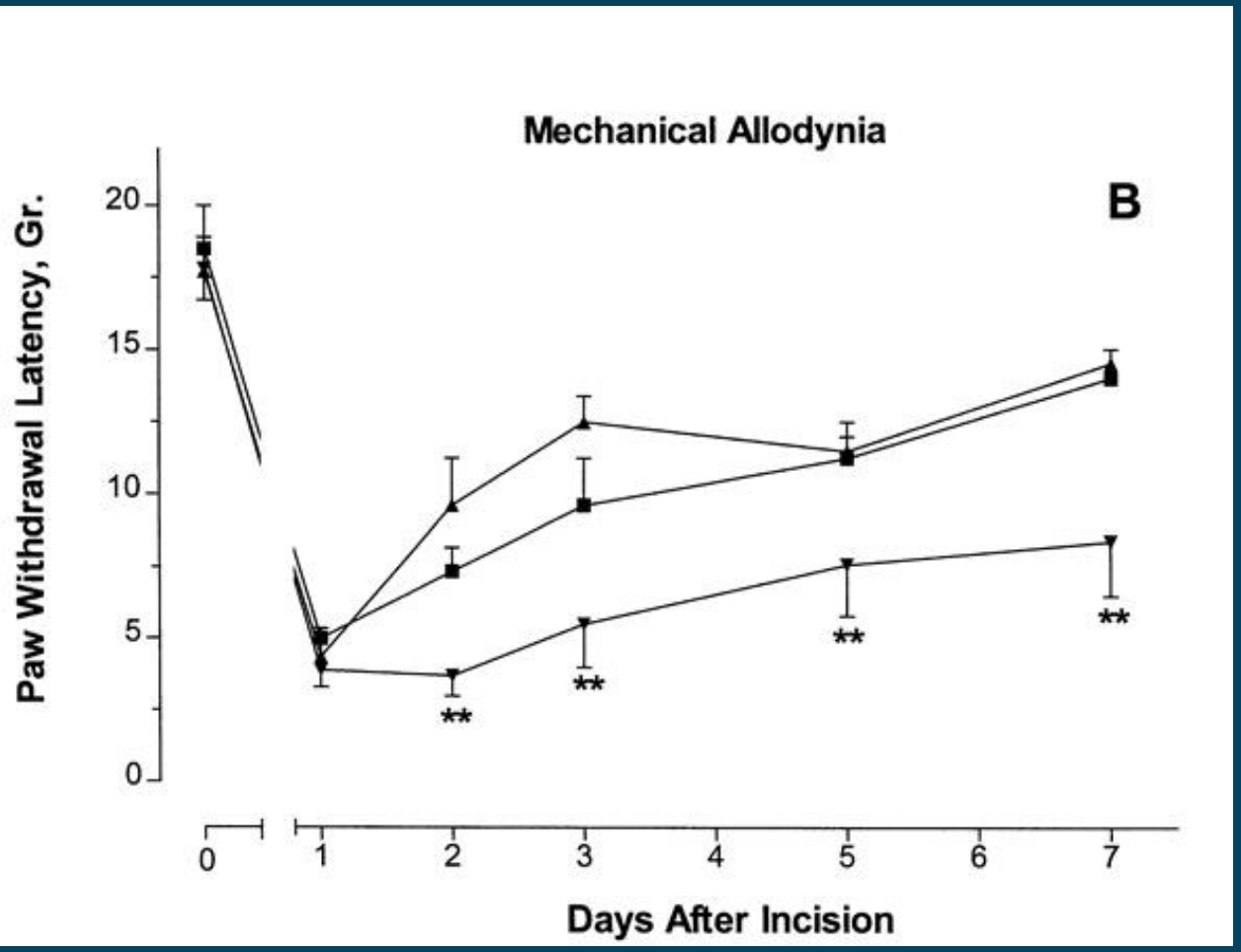
Square - Control (incision only)

Triangle up - Morphine and Naloxone pre incision, morphine post incision

Triangle down - Morphine and naloxone pre incision, nothing post incision

Li, Angst. Anesth Analg, 2001.

Animal Studies



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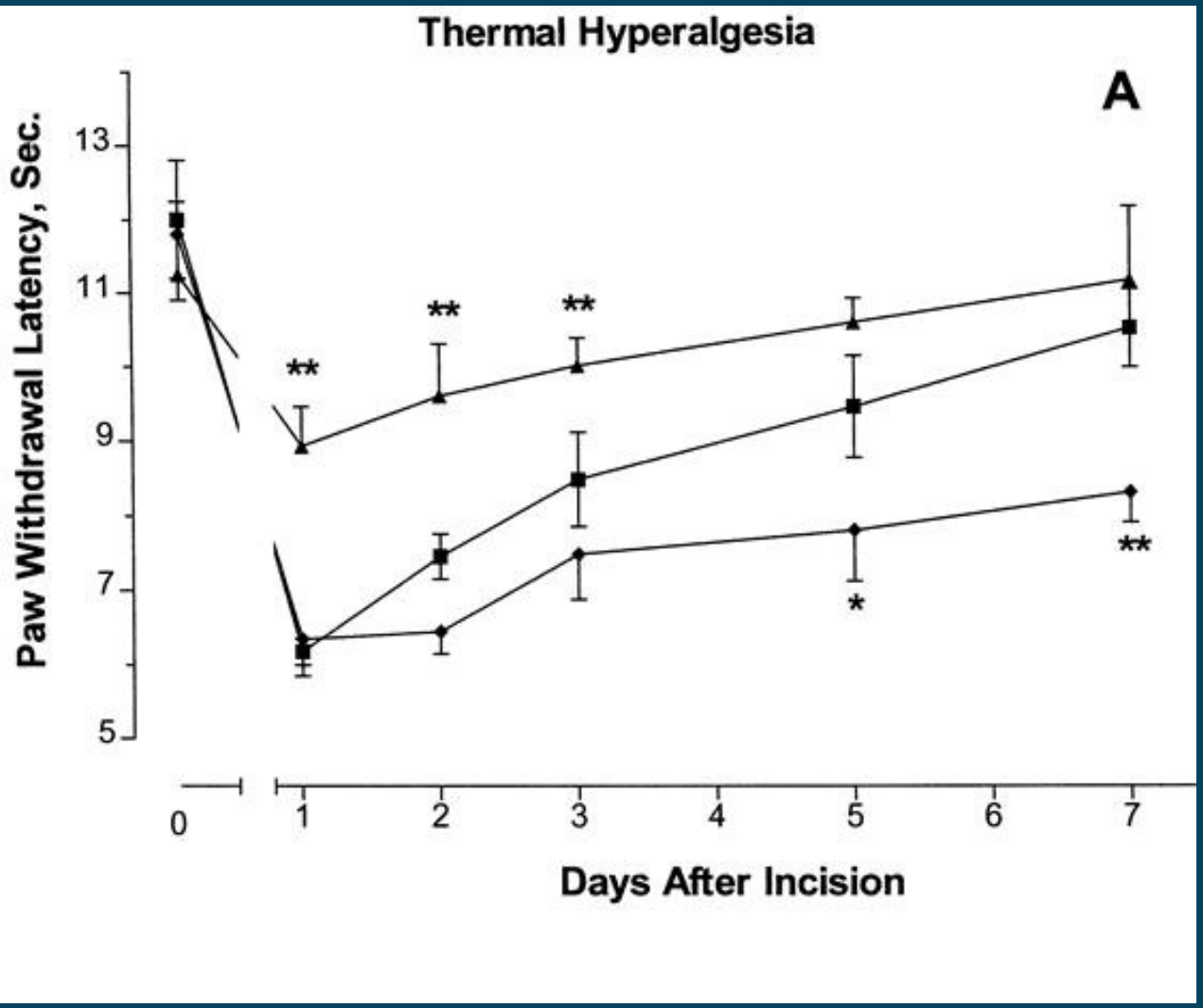
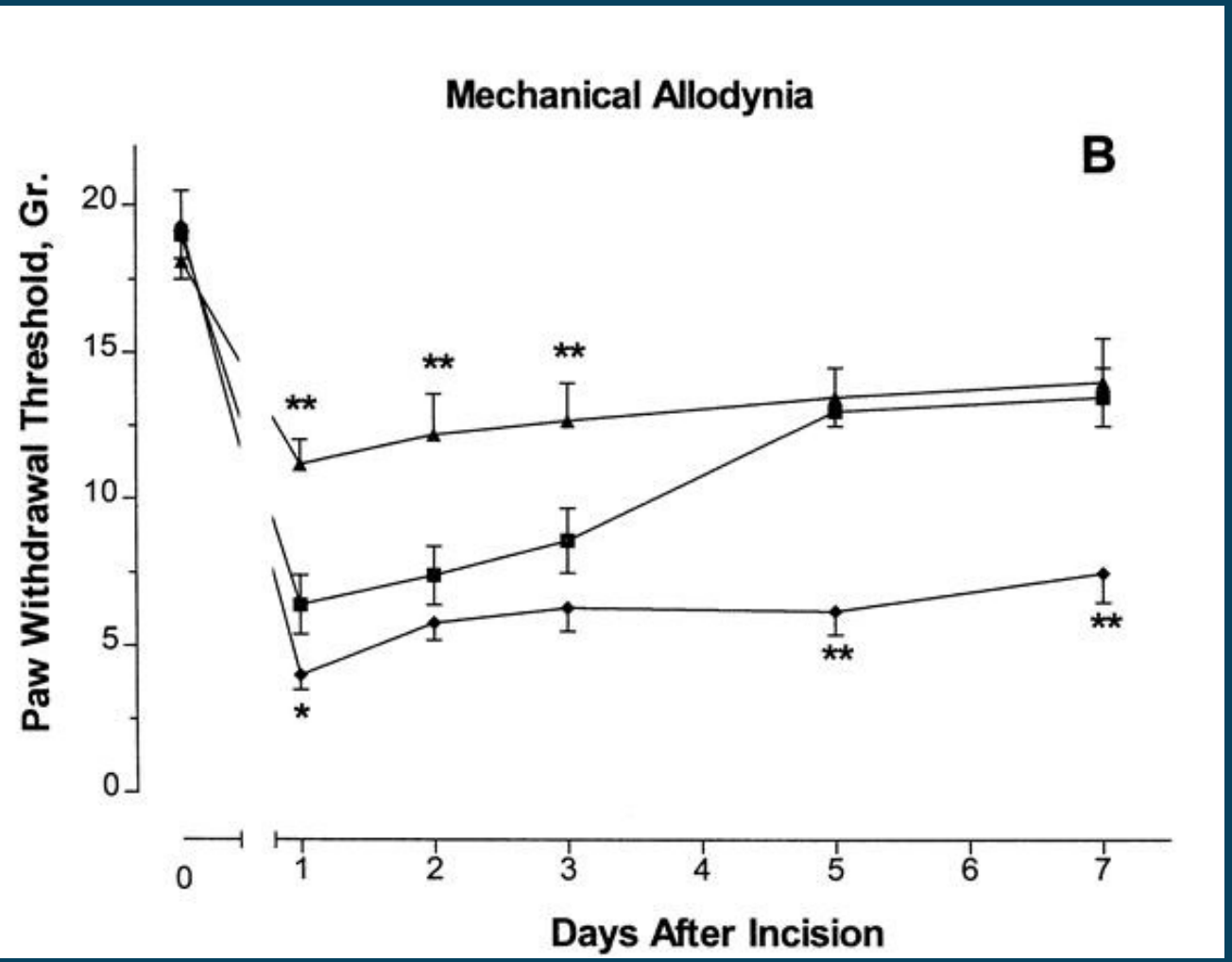


Squares - Control

Triangles - Naloxone Pump

Diamonds - Naloxone bolus before testing

Animal Studies



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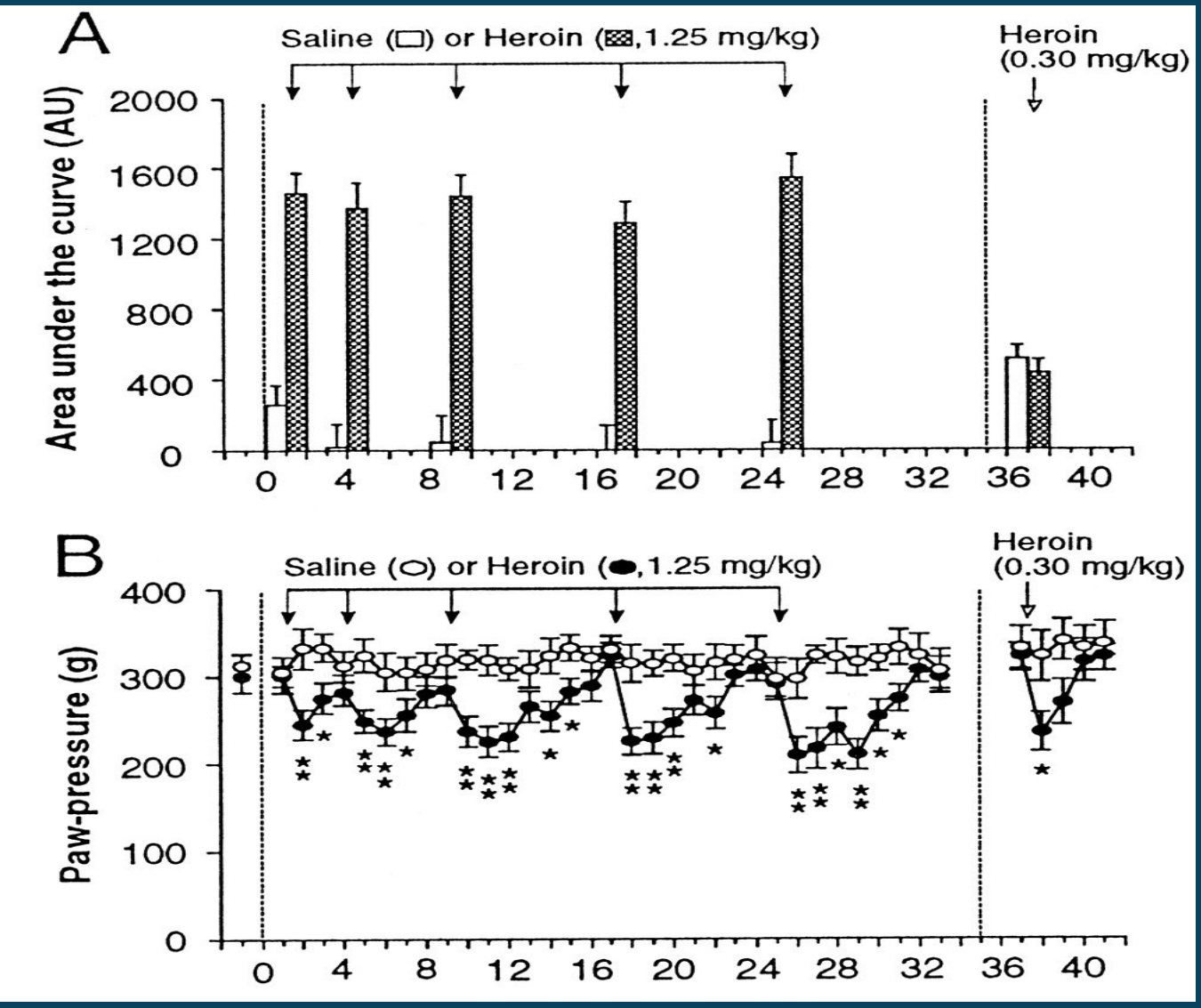
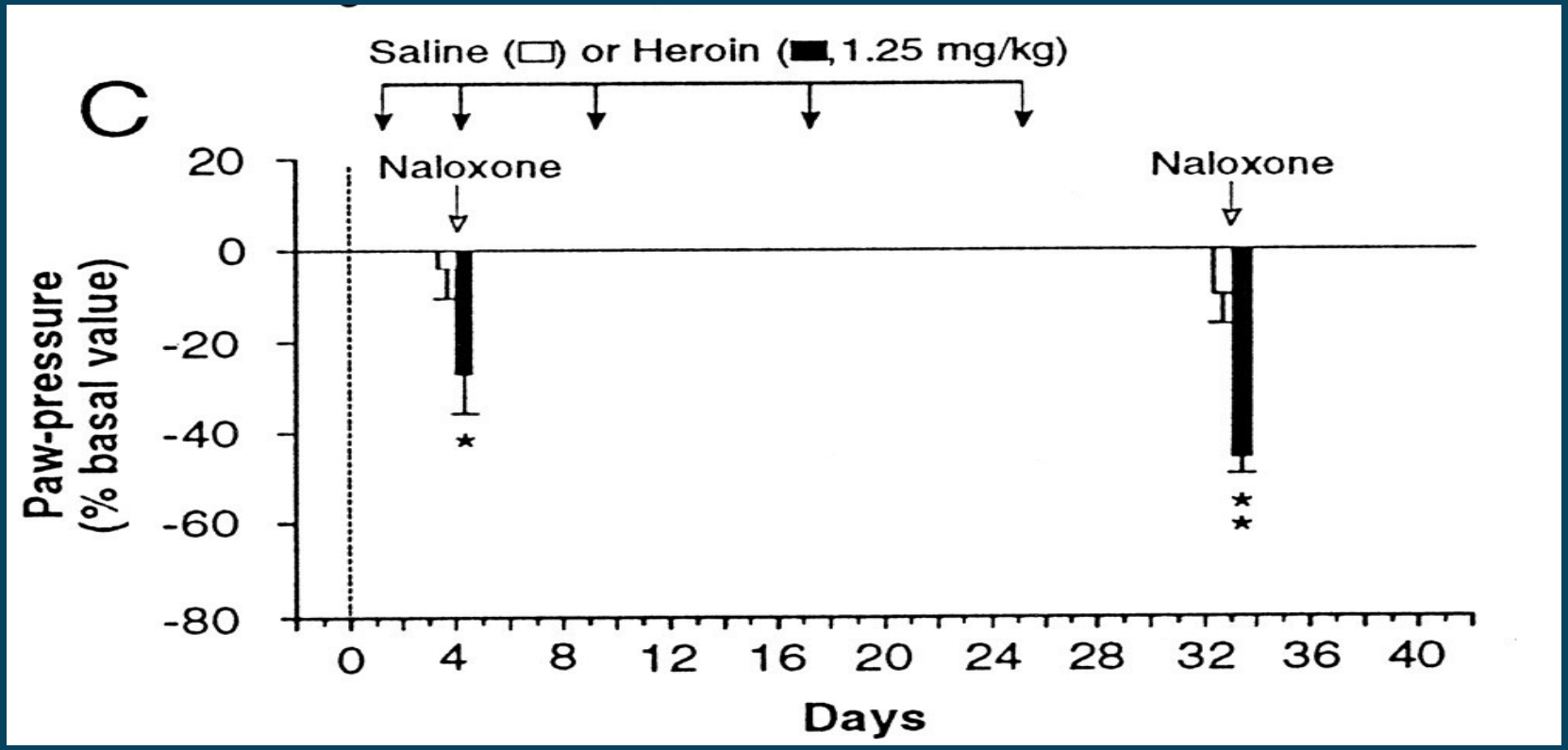


Graph A - Analgesic Efficacy

Graph B – Pain tolerance

Celerier et al. Journal of Neuroscience,

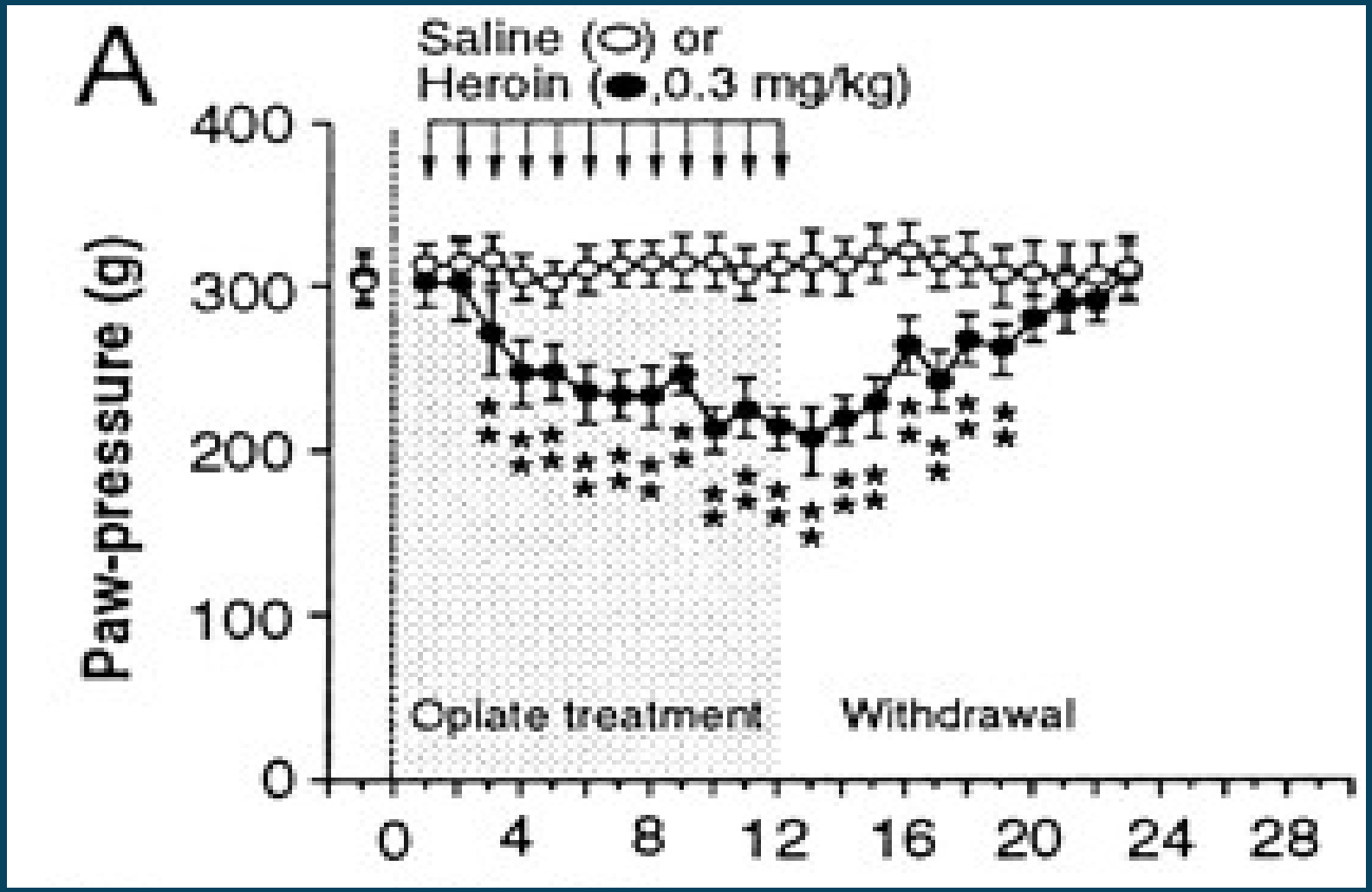
Animal Studies



Celerier, et al. 2001

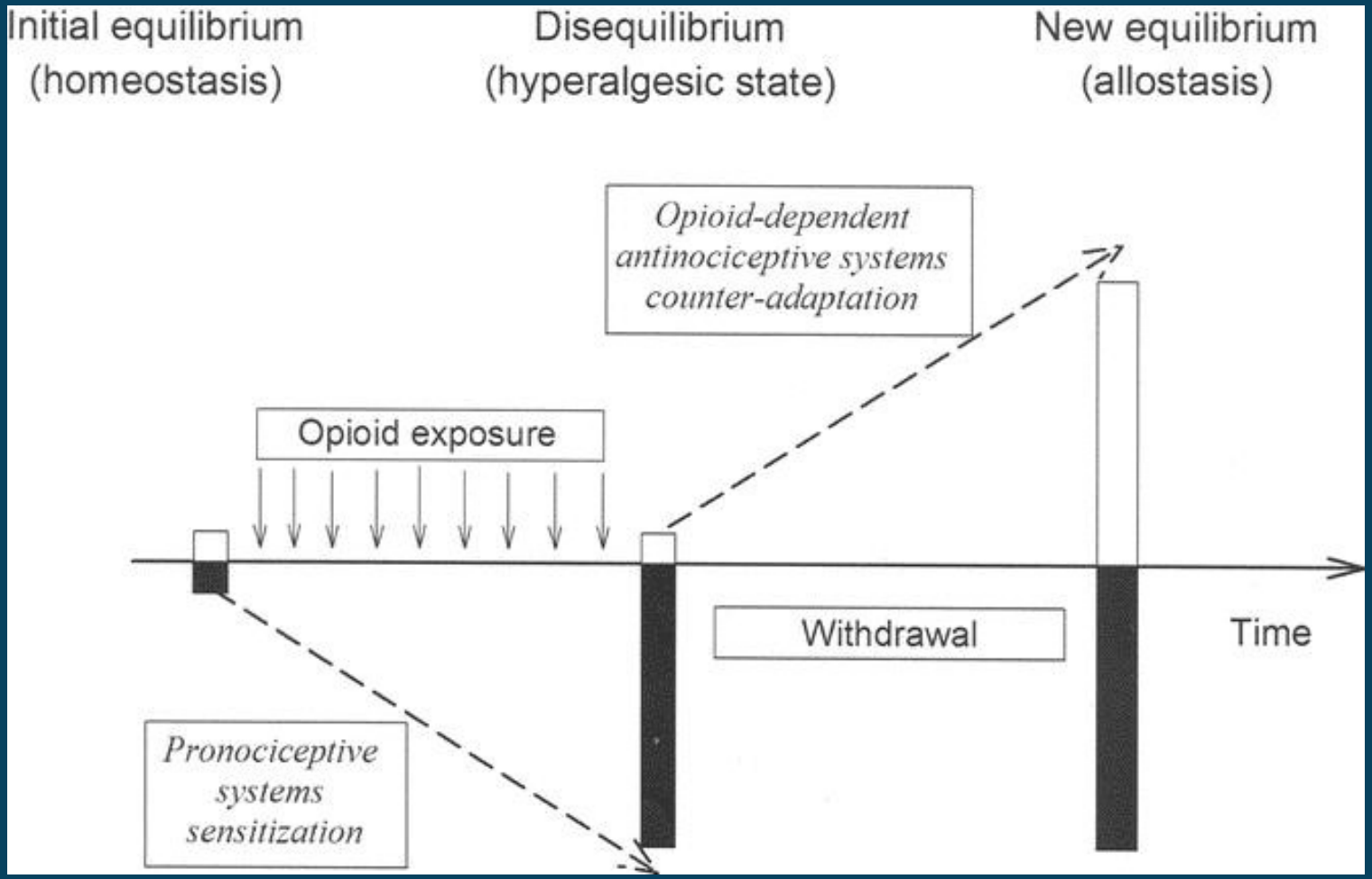
Celerier et al. Journal of Neuroscience,

Animal Studies



Celerier et al. Journal of Neuroscience, 2001.

Animal Studies



Celerier et al. Journal of Neuroscience, 2001.

Animal Studies Summary

- Opioid therapy leads to a hyperalgesic state.
- This hyperalgesic state is additive with pain and hyperalgesia from further stimuli including surgical incisions.
- Repeated or continued opioid exposures lead to an increase in both magnitude and duration of this state.
- The hyperalgesic state persists beyond the period of opioid administration.
- After the resolution of hyperalgesia, administration of an opioid or opioid antagonist causes a recurrence of hyperalgesia

Human Studies – Methadone Maintenance

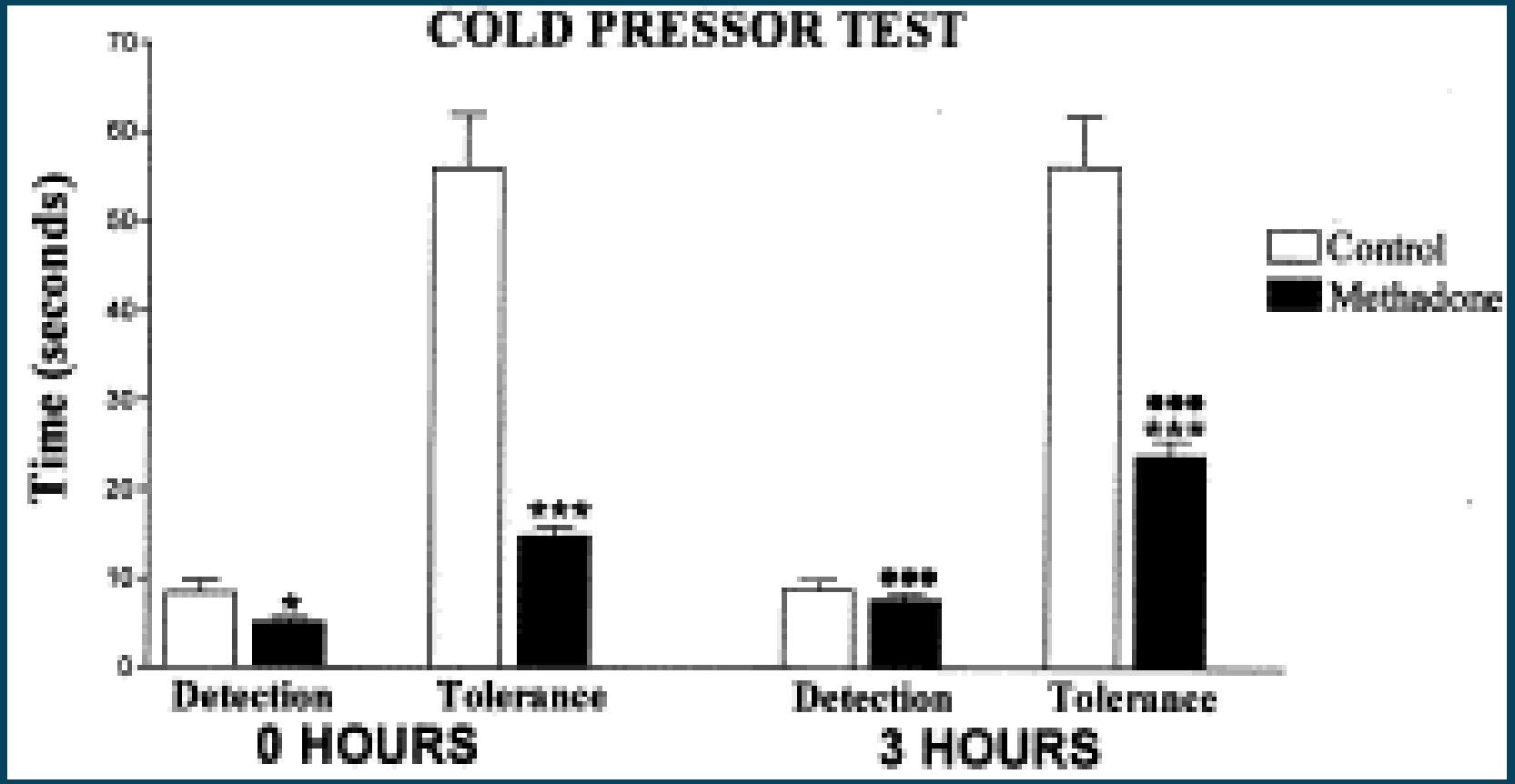
Reference No.	Study Population (n)	Methadone: Daily dose (mg)*	Methadone: Duration (mo)*	Pain: Test	Pain: Threshold	Pain: Tolerance	Remarks
11	43 patients receiving methadone; 26 patients not receiving methadone	—	—	CPP	—	42% ↓ †	Similar findings in current and former cocaine users
15	42 patients; 16 controls	0.7 ± 025 (mg/kg)	3–56	PP	ND	—	
14	18 patients; 10 controls	7.5–130	6–120	EP	ND‡	—	
10	60 patients; 60 controls	66 ± 20	>1	CPP	—	53% ↓ ‡	
13	18 patients; 18 controls	66 ± 21	>1	CPP	—	56% ↓ ‡	
12	16 patients; 16 controls	62 ± 6	4–120	CPP EP	43% ↓ § ND	74% ↓ § 15% ↓	At peak plasma concentration, no hyperalgesia for EP and 57% ↓ for CPP
9	4 patients; 4 controls	81 ± 25	9–96	CPP EP	34% ↓ § ND	76% ↓ § ND	At peak plasma concentration, 56% ↓ for CPP

* Mean ± SD or range. † Time of testing relative to time of drug intake not specified. ‡ Measurements obtained within 2 h of drug administration. § Measurements obtained at trough plasma concentrations.

— = no data available; ↓ = decrease compared with controls; CPP = cold pressure pain evoked by ice-water immersion of hand; EP = electrically induced pain at earlobe; ND = no difference; PP = blunt pressure pain evoked on middle phalanx of digit.

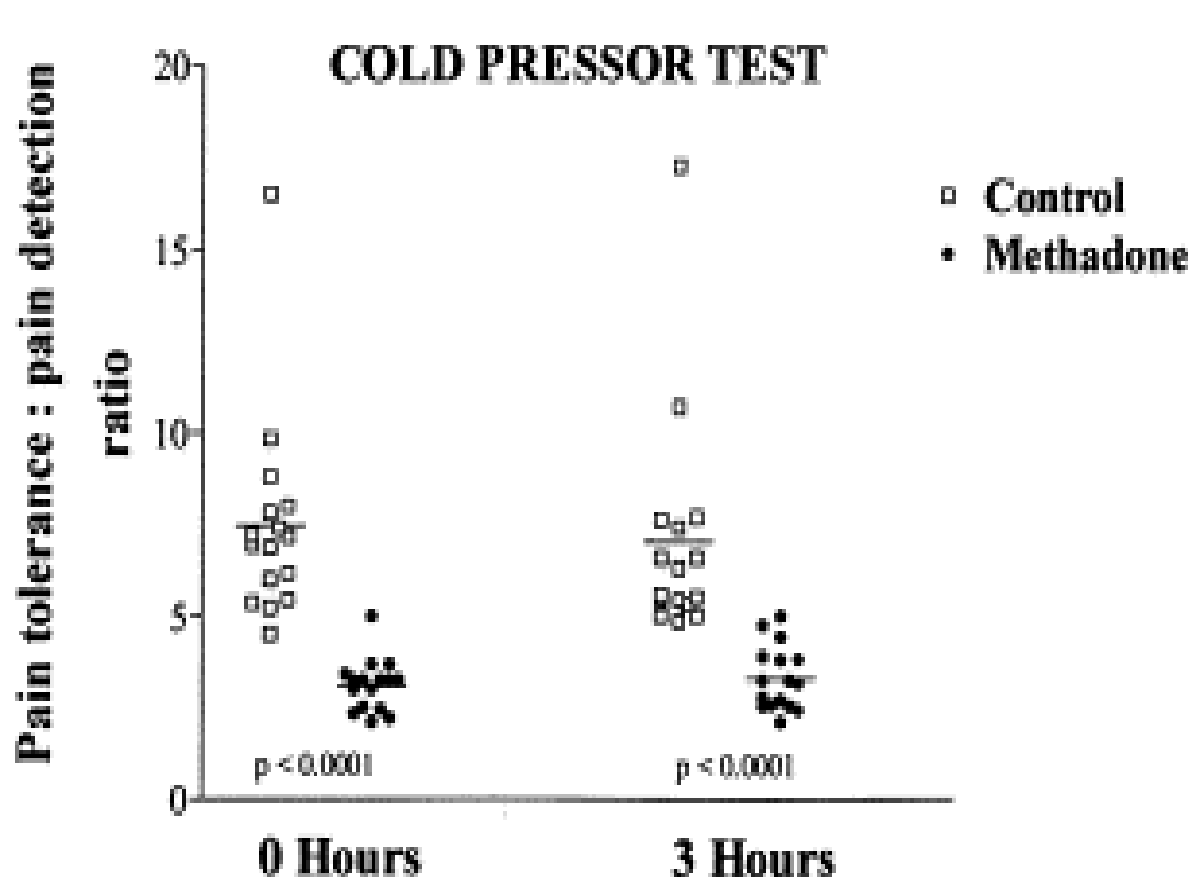
Angst, Anesthesiology 2006.

Human Studies – Methadone Maintenance



Doherty, et al. Pain 2001.

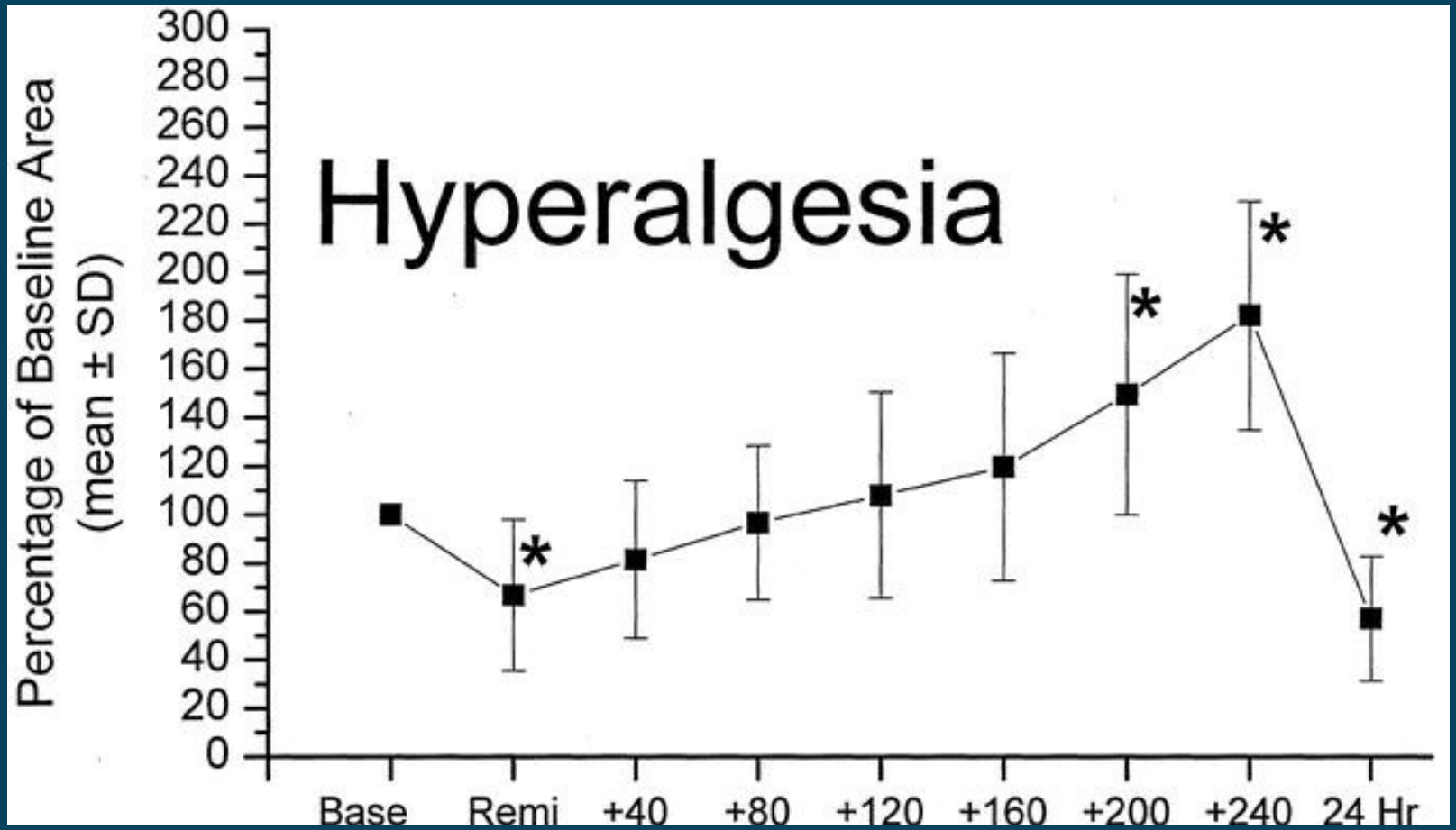
Human Studies – Methadone Maintenance



Doherty, et al. Pain 2001.

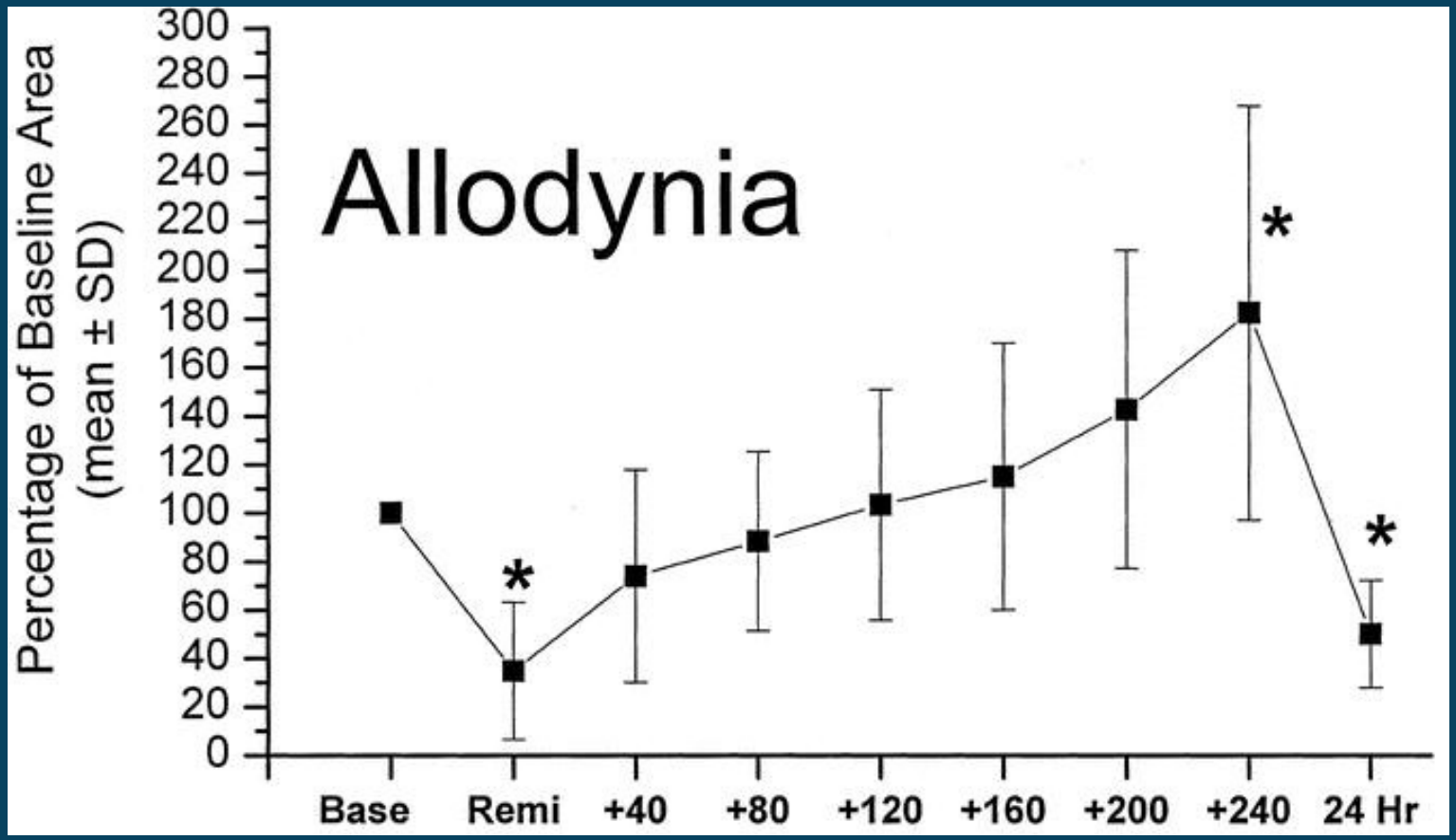
Human Studies – Volunteer

Human Studies – Volunteer



Hood et al. Anesth Analg 2003.

Human Studies – Volunteer



Hood et al. Anesth Analg 2003.

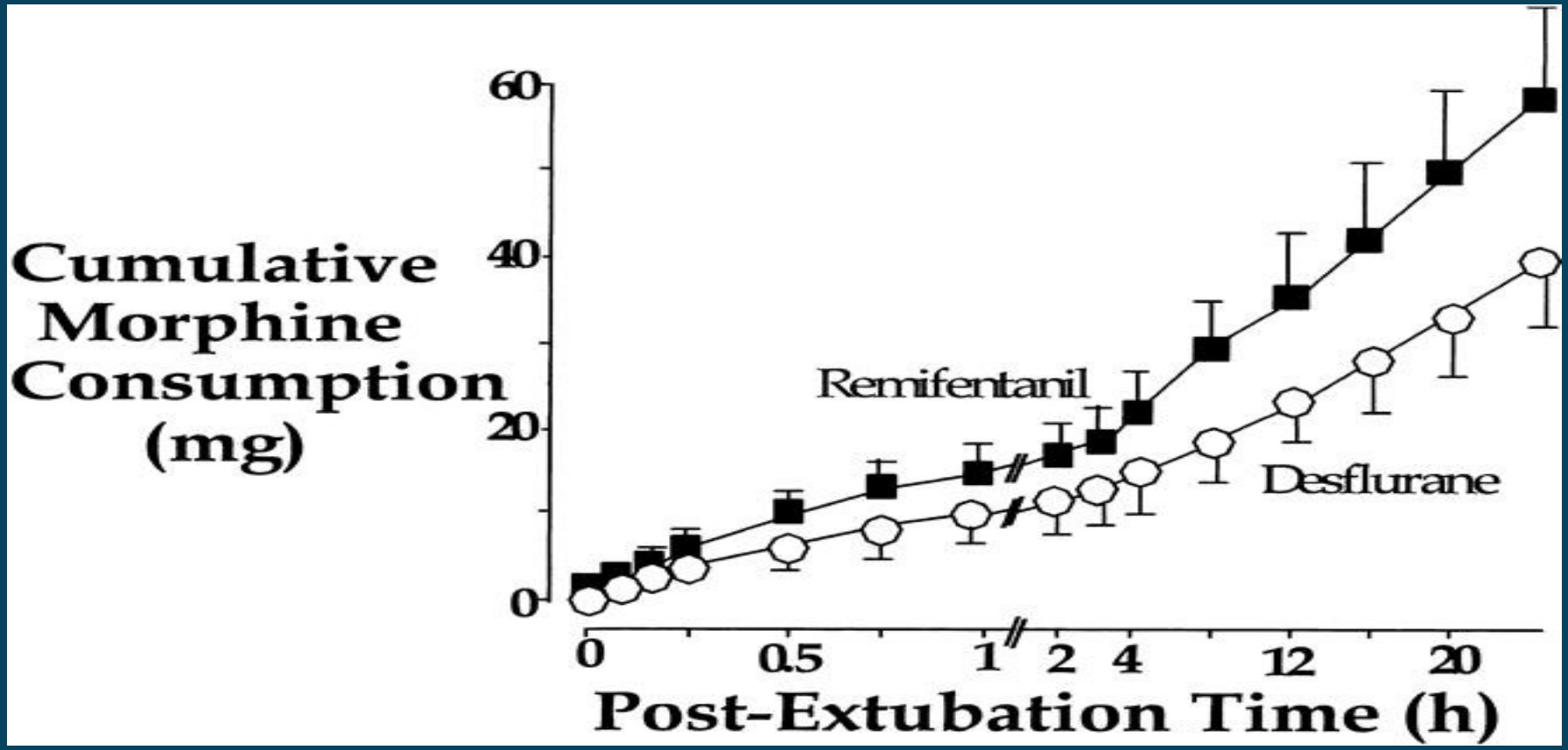
Human Studies – Intraoperative Opioids

	Intraoperative Data		(High *vs.* Low Intraoperative Opioid Dose)		
Surgery	Opioid	Dose	Opioid Use	Pain	Remarks
Cesarean section	Fentanyl IT	0 *vs.* 25 μg	60% ↑	ND	n = 60; 23-h observation
Hysterectomy	Fentanyl IV	1 *vs.* 22 μg/kg	120% ↑	30% ↑	n = 60; 16-h observation
Colectomy	Remifentanil IV	0.1 *vs.* 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 260 min	85% ↑	50% ↑	n = 50; 24-h observation
Gynecologic	Remifentanil IV	0.1 *vs.* 0.23 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 100 min	ND	ND	n = 60; 24-h observation

IV = intravenous; ND = not different.

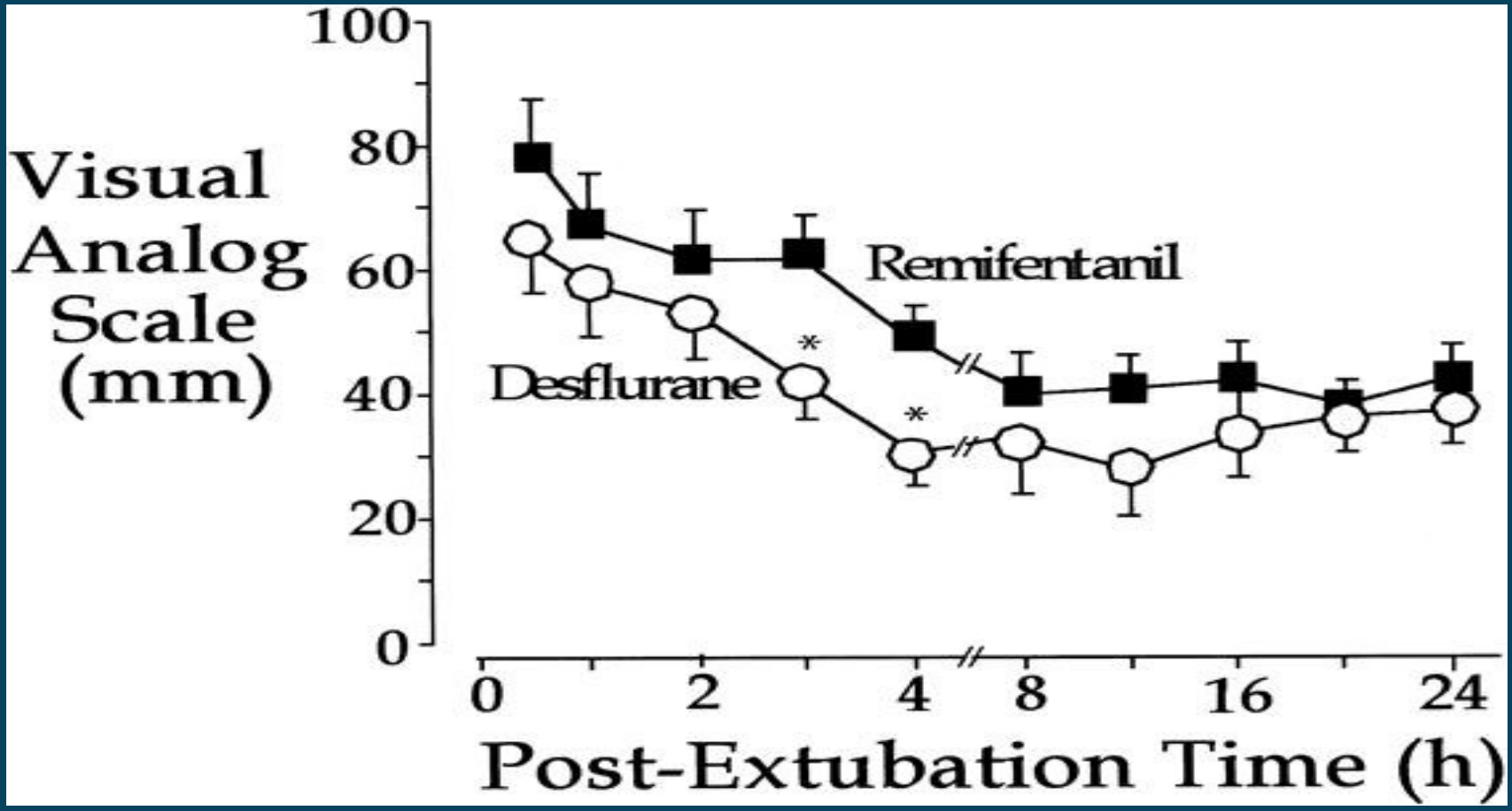
Angst, Anesthesiology 2006.

Human Studies – Intraoperative Opioids



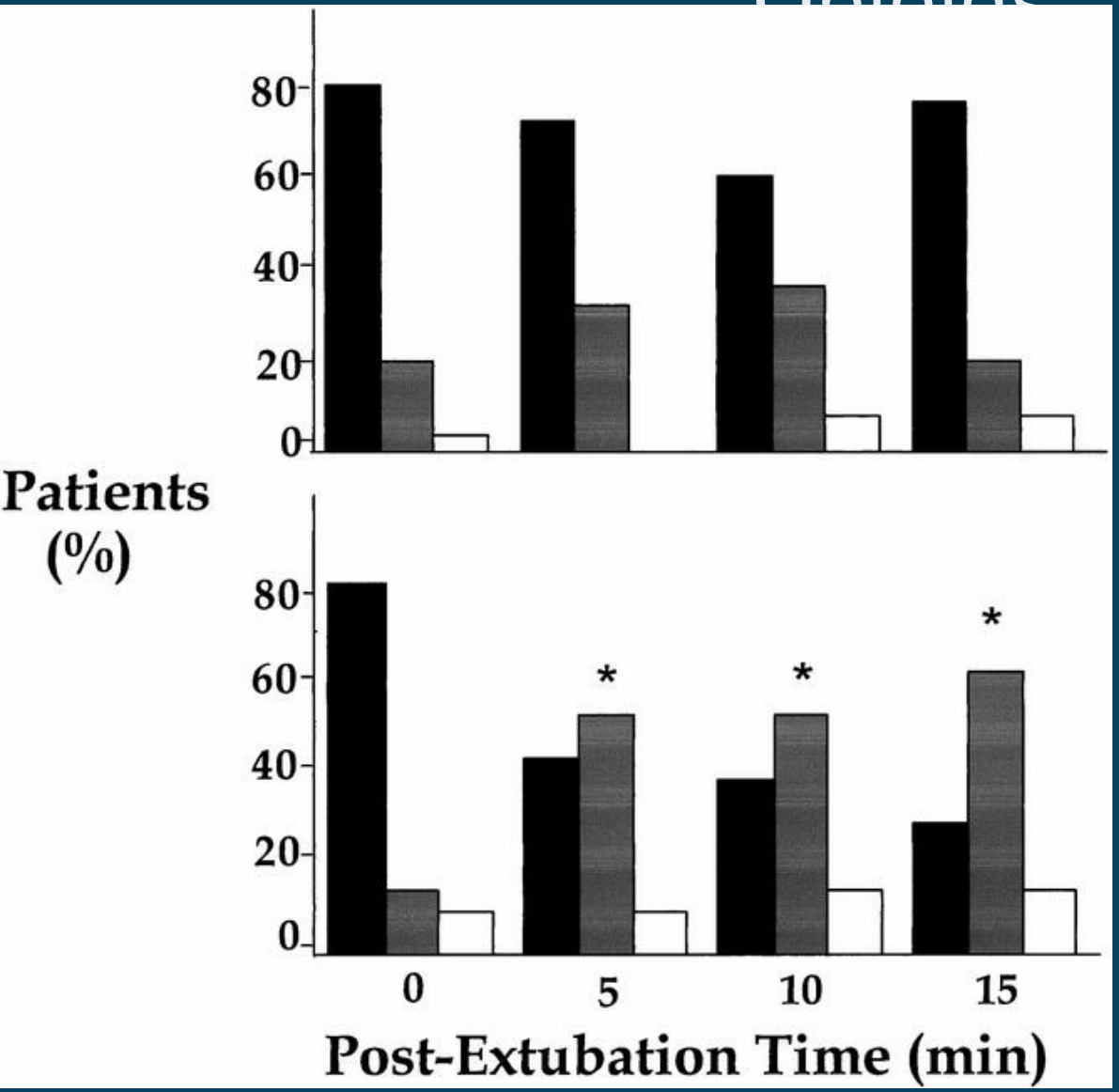
Guignard et al, Anesthesiology

Human Studies – Intraoperative Opioids



Guignard et al, Anesthesiology

Human Studies – Intraoperative Opioids



Lower dose opioids – top rows

Higher dose opioids – bottom rows

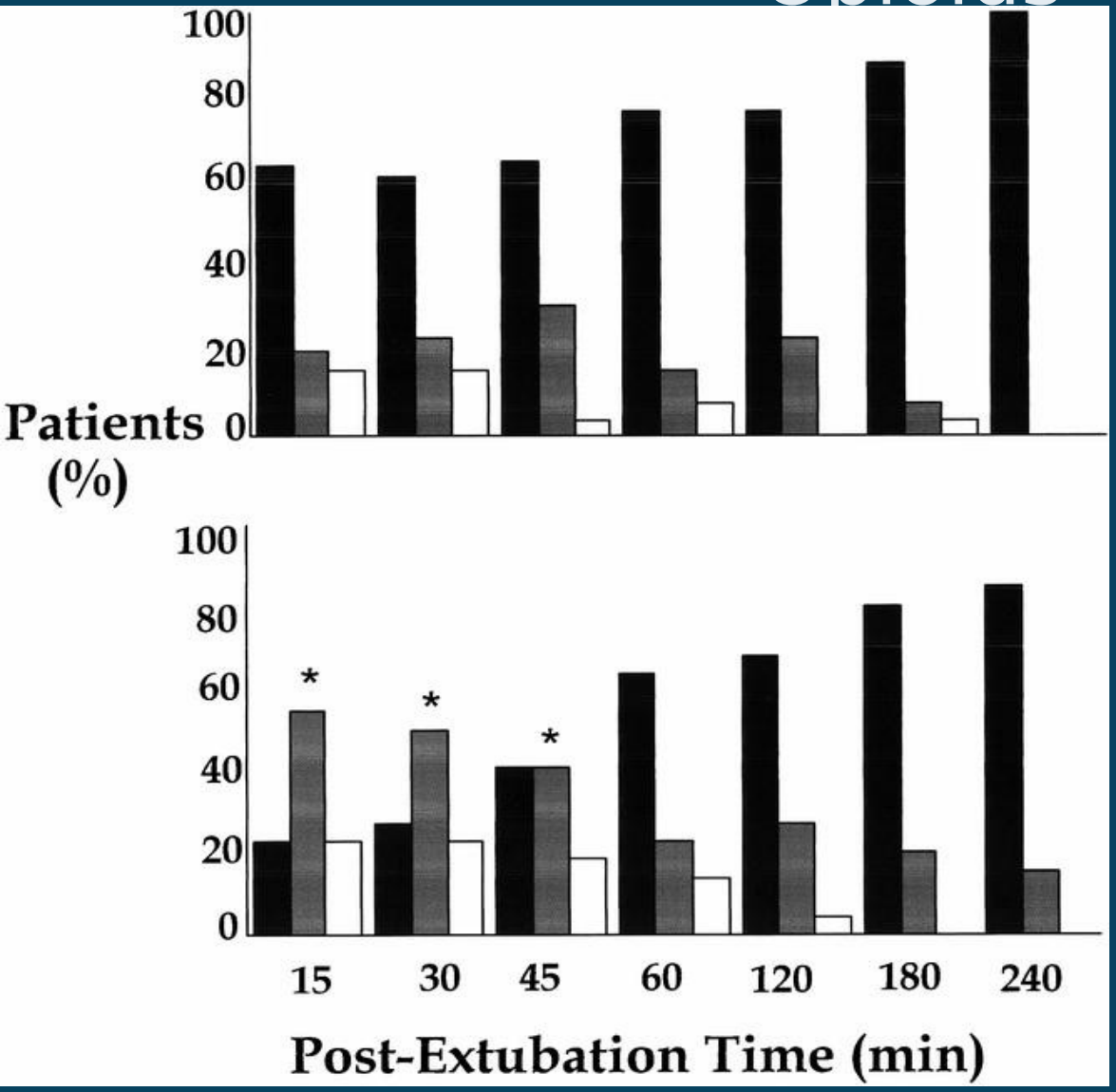
Black Box – Comfortable

Gray Box – Verbal Expression moderate pain

White Box – Verbal/behavioral expression of severe pain

Guignard et al, Anesthesiology

Human Studies – Intraoperative Opioids



Lower dose opioids – top rows

Higher dose opioids – bottom rows

Black Box – Comfortable

Gray Box – Verbal Expression moderate pain

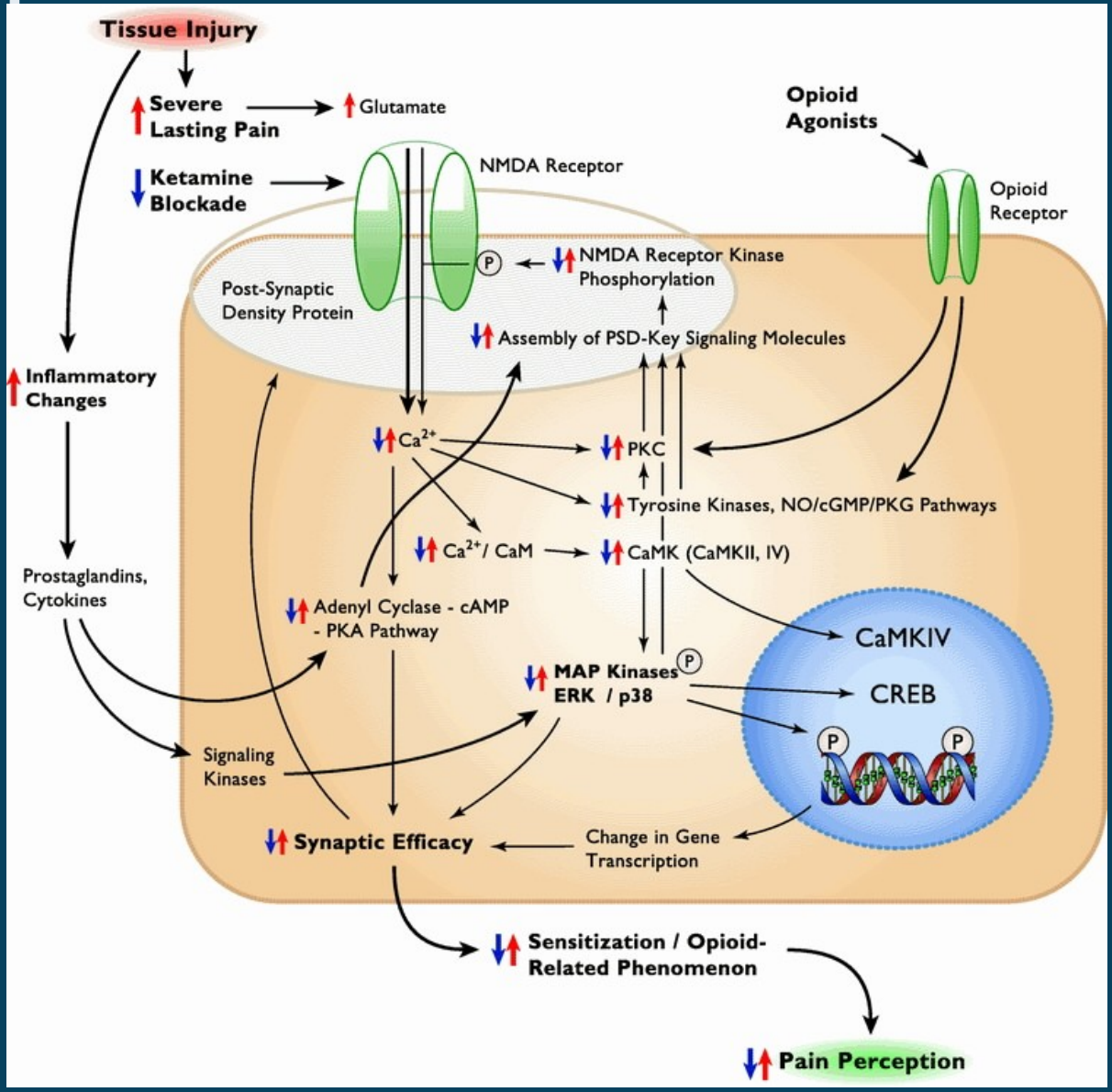
White Box – Verbal/behavioral expression of severe pain

Guignard et al, Anesthesiology

Human Studies - Summary

- Patients on chronic methadone display decreased pain tolerance at both peak and trough opioid levels.
- Higher intraoperative opioid doses lead to increased post operative pain and opioid consumption.
- Periods of opioid analgesia are followed by hyperalgesia and allodynia.

Opioid NMDA Interactions

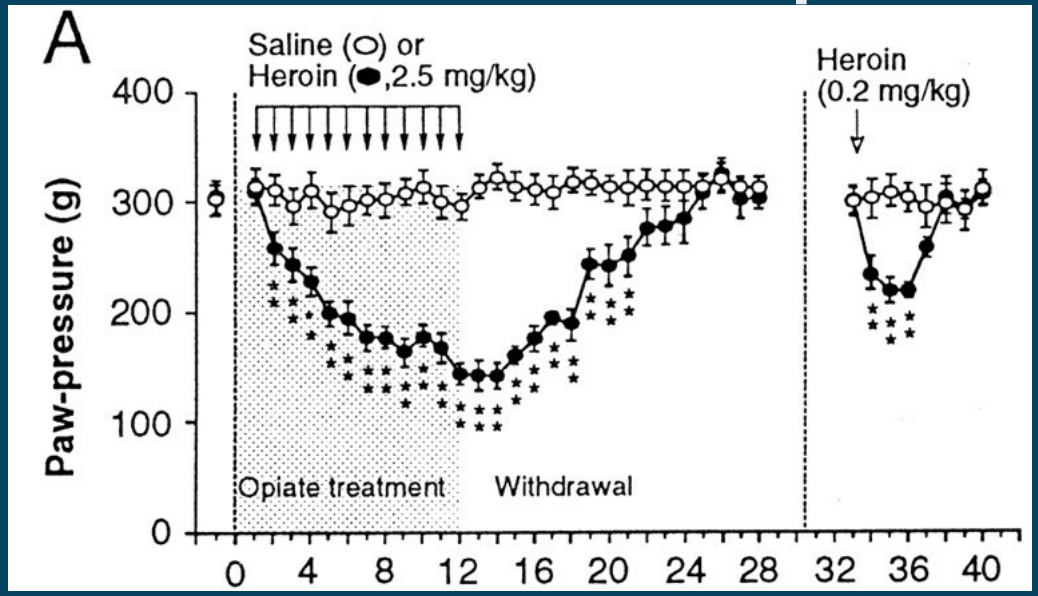


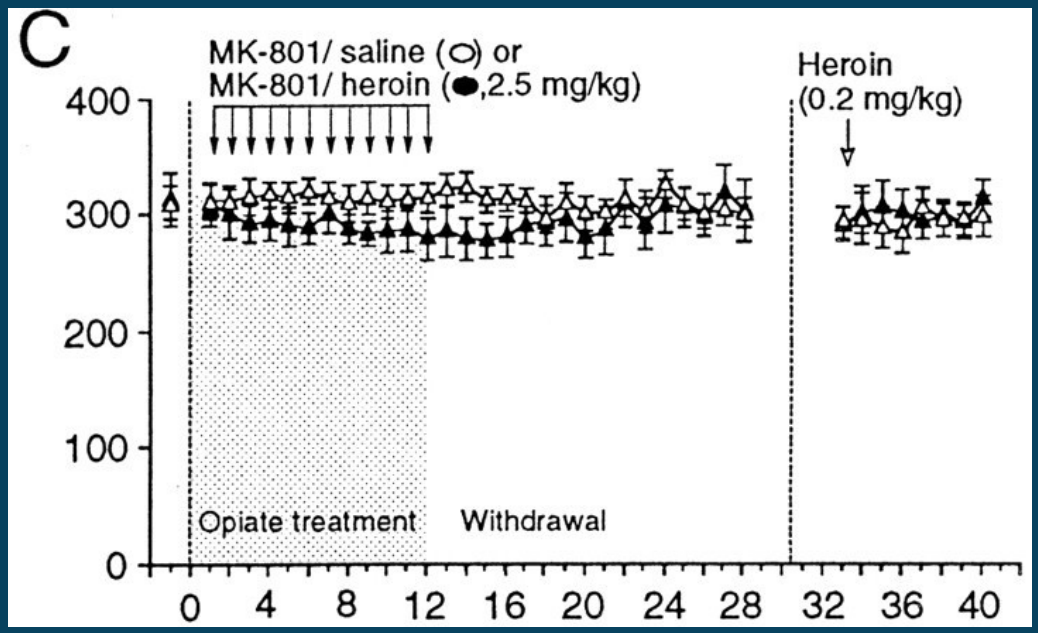
Weiskopf Anesthesiology. 2005.

Opioid/NMDA Interactions

- NMDA and Opioid receptors share similar distributions in the CNS mainly post synaptic neurons in the hippocampus, cortex, thalamus, brainstem, especially dorsal horn laminae I and II.
- Opioid receptor activation initiates multiple events leading to post synaptic neuronal hyperpolarization ie decreased transmission.
- NMDA Receptors do not normally participate in nociception but can be activated by opioid signalling mechanisms, augmented nocideptive input and the inflammatory cascade.
- Once activated, NMDA receptor cascades increase synaptic transmission as well as further augment NMDA receptor transmission.
- NMDA receptor antagonism can prevent opioid tolerance and restore the antinociceptive activity of opioids.

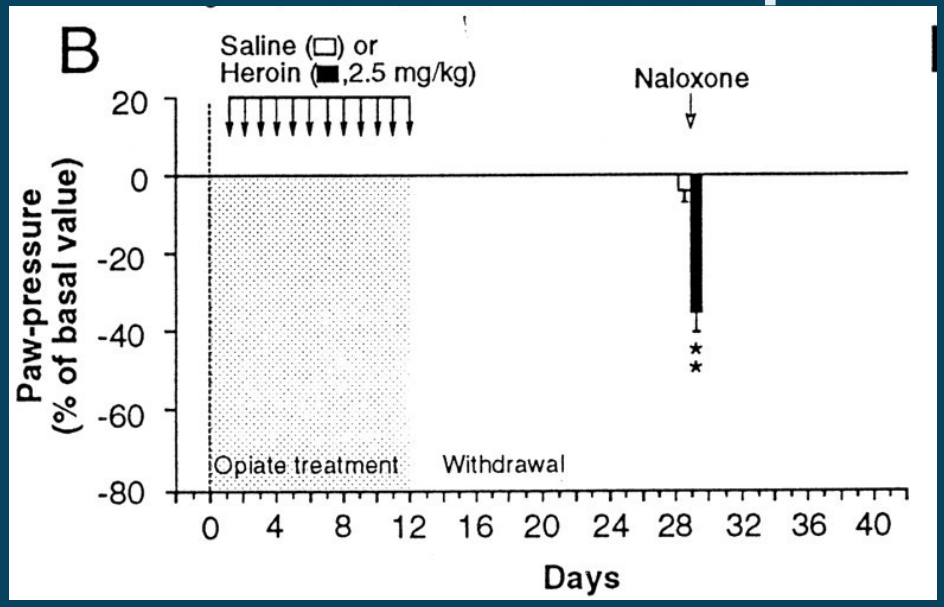
NMDA Receptor Antagonism

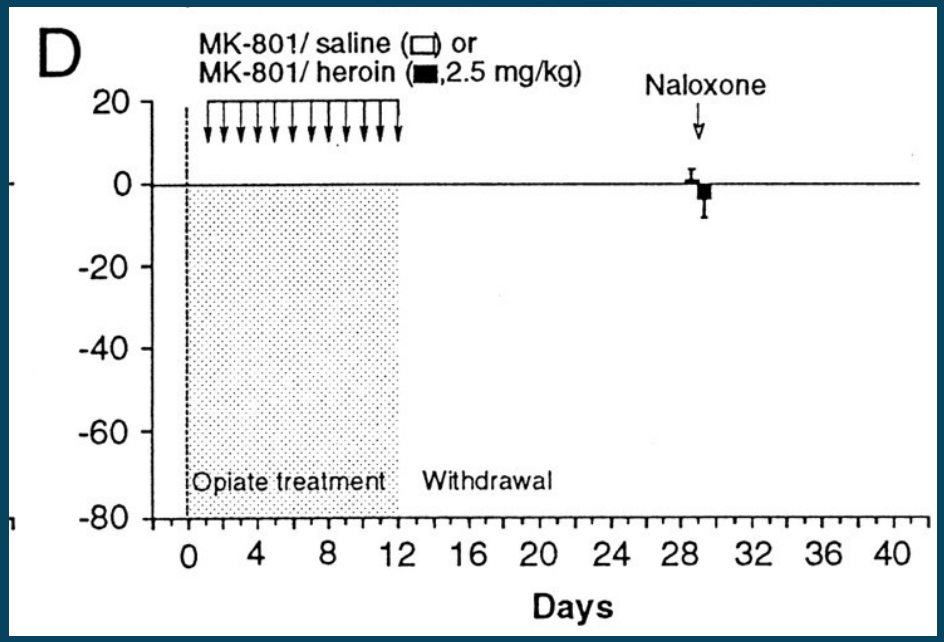




Celerier et a l. J. Neuroscience 2001.

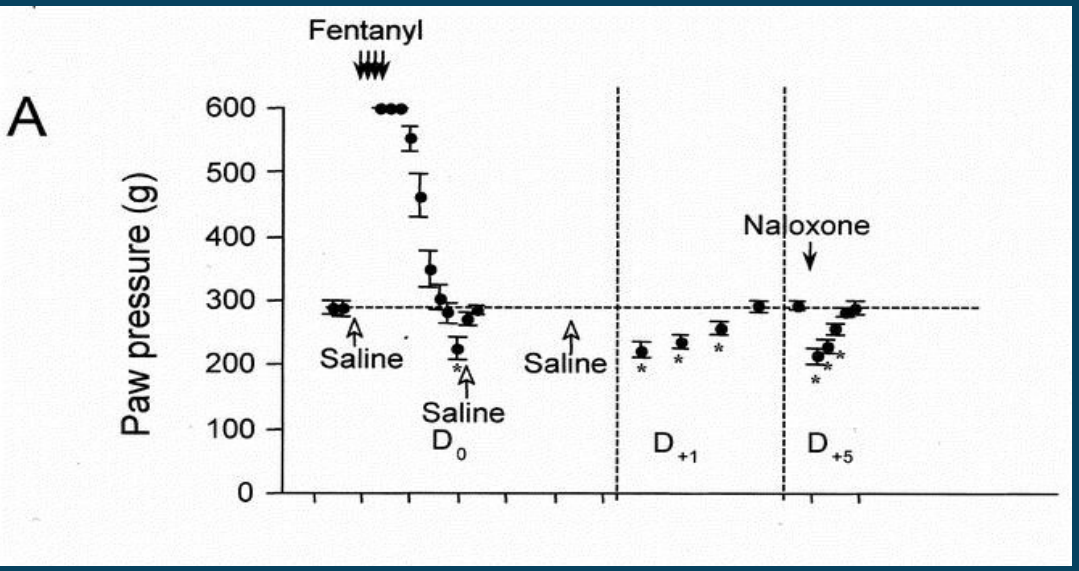
NMDA Receptor Antagonism

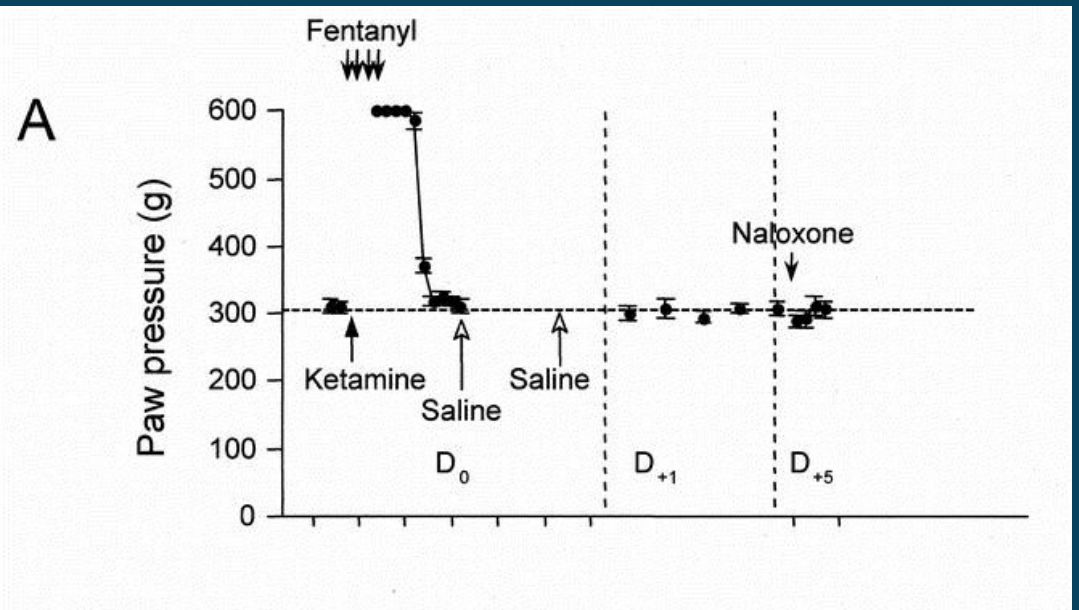




Celerier et a l. J. Neuroscience

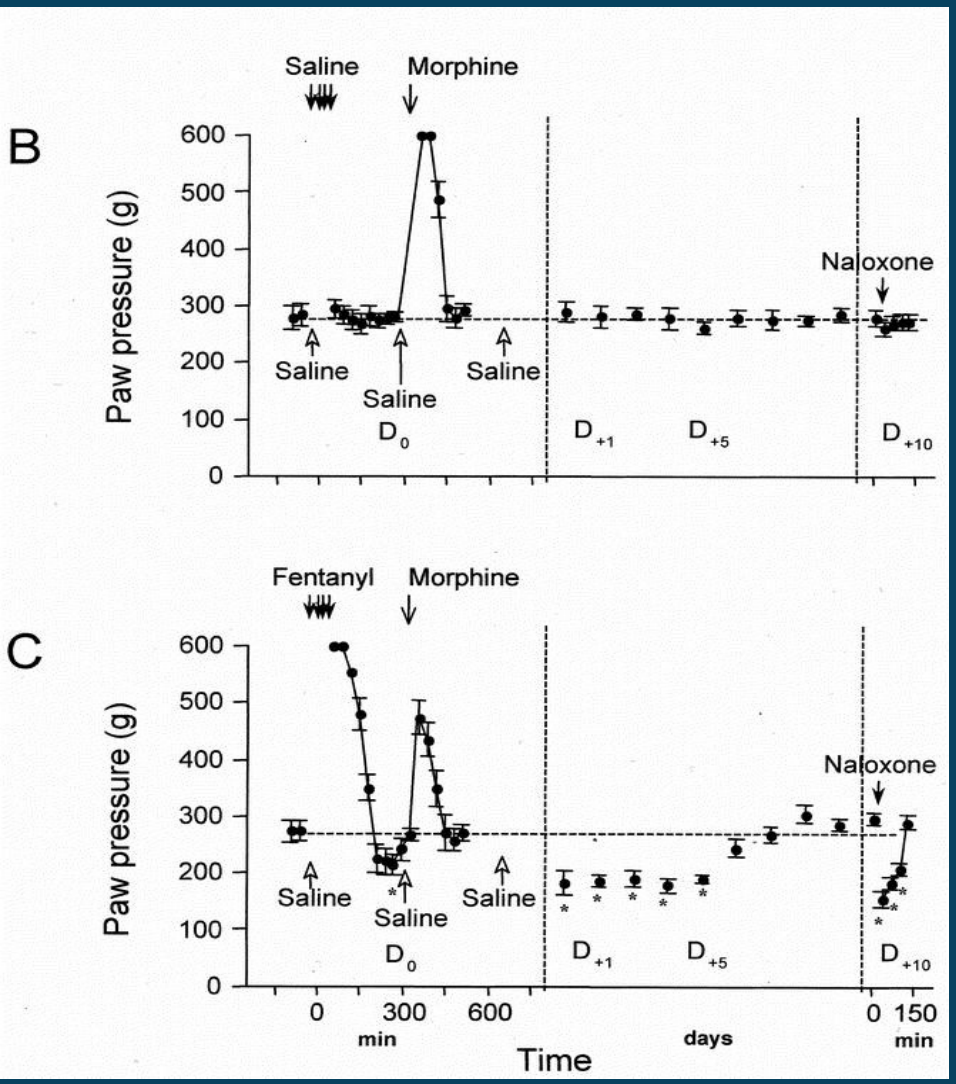
NMDA Receptor Antagonism

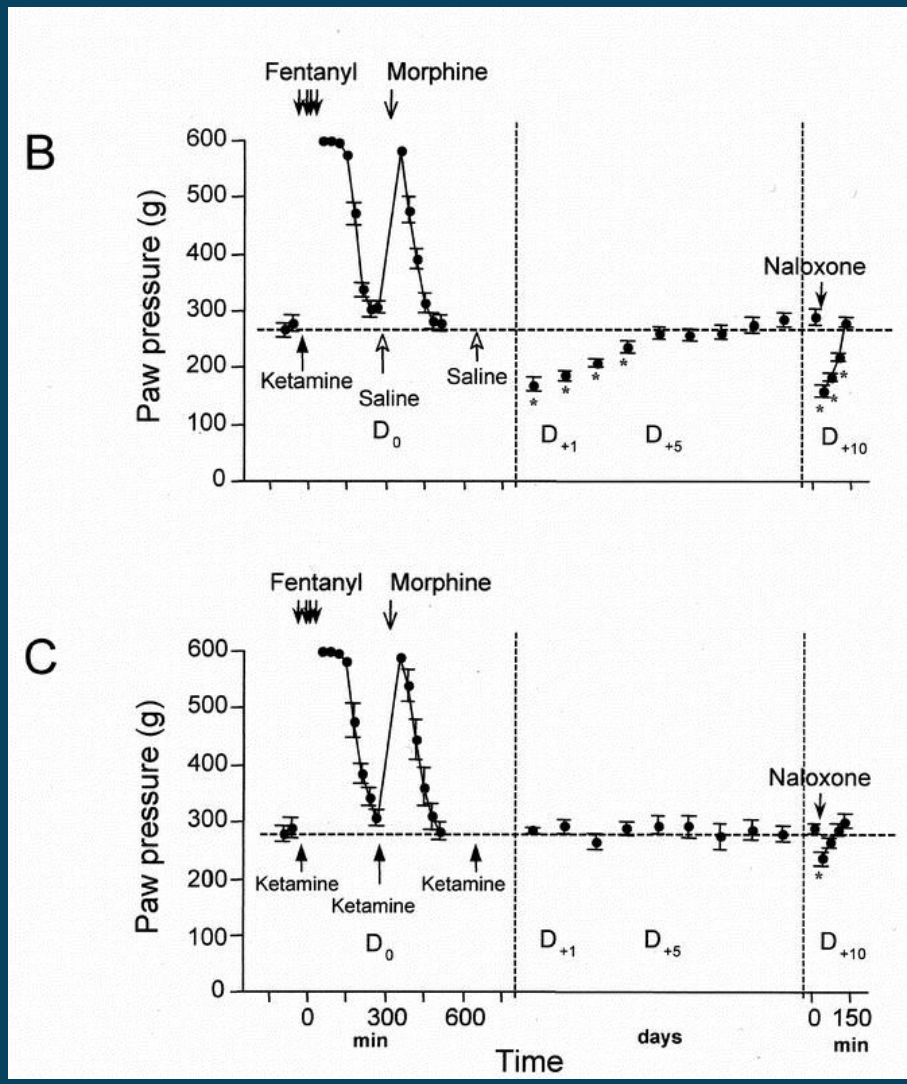




Laurin et al.
Anesth Analg
2002

NMDA Receptor Antagonism





Laurin et al.
Anesth Analg
2002

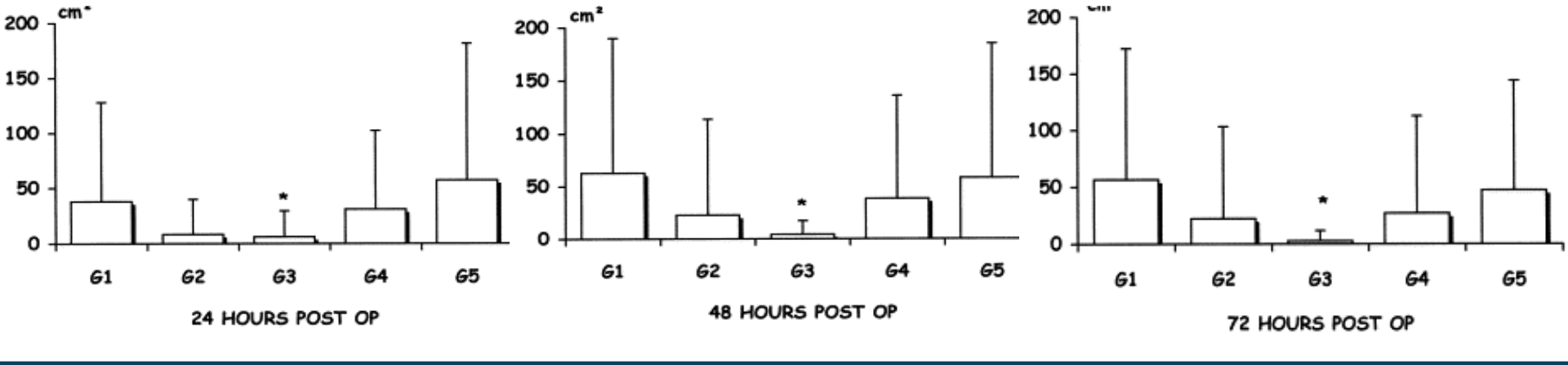
Intraoperative Studies

Subanesthetic Ketamine as an adjunct to Regional and General Anesthe

Reference	Quality Score	Size / Study Group	Study Setting / Anesthesia	Ketamine, Administration Schedule	Difference in Postoperative Outcome Measures after iv Ketamine	Difference in Side Effects after Ketamine	Comment
Menigaux et al.[9] 2001	5	25/25 C/pre	outpatient knee arthroscopy / GA, + pre-closure intraarticular LA and opiate	racemic, iv: 0.15 mg/kg	↓pain at rest / on mobilization, postop day 0,1,2 ↓analgesic need ↑walking ability, postop day 1	NS	↑early procedure-related functional outcome
Kwork et al.[10] 2004	5	45/45/45 C/preop/post	gynecologic laparoscopic surgery / GA	racemic, iv: 0.15 mg/kg preincisional or after wound closure	preincisional ketamine: ↓ pain over 6 h postop ↑ time to first analgesic request ↓ postop analgesic need	NS	one Ket dose, injected before opiate / trends for better recovery
Stubhaug et al.[11] 1997	5	10/10 C/pre	life kidney donation / GA + pre-closure intercostal LA	racemic, iv: 0.5 mg/kg preincisional + 120 µg/kg/h for 24 h + 60 µg/kg/h for 48 h	↓ mechanical hyperalgesia, postop day 1, 3, 7 ↓ wind-up pain, postop day 3 ↓ pain first h postop ↑ patient satisfaction	↓ PONV, postop day 1	↓pathologic pain
Aida et al.[12] 2000	4	31/30/29/31 C/EA/pre/EApre	gastrectomy / GA, or GA + intraop EA with opiate	racemic, iv: 1 mg/kg preincisional + 0.5 mg/kg/h intraop	best treatment: EA and ketamine, ↓ pain at rest / on movement, postop day 1, 2 ↓ analgesic need, postop day 1, 2	NS	↓effective analgesia after GA + Ket than after GA, EA + Ket
de Kock et al.[13] 2001	5	20/20/20 C/epi-prelow/high /20/20 /iv-prelow/high	adenocarcinoma surgery / GA + intraop EA with LA, opiate, and clonidine	racemic, epidural or iv (low or high): 0.25 or 0.5 mg/kg preincisional + 125 or 250 µg/kg/h intraop	best treatment: high dose iv ketamine, ↓ analgesic need, postop day 1-3 ↓ wound hyperalgesia, postop day 1-3 ↓ residual pain until 6th postop month	NS	↑long-term outcome ↓long-term pain after surgery
Karamaz et al.[14] 2003	5	20/20 C/preop	renal surgery / GA + intraop EA with LA and opiate	racemic, iv: 0.5 mg/kg preincisional + 0.5 mg/kg/h intraop	↓ pain at rest for 6 h postop ↑ time to first analgesic request ↓ analgesic need, postop day 1, 2	↓postop nausea and pruritus	Ket injected during induction of GA
Snijdelaar et al.[15] 2004	5	14/14 C/preop	radical prostatectomy / GA	S+, iv: 100 µg/kg preoperative + 120 µg/kg/h intraop + postop PCA, bolus: 1 mg morphine, 0.5 mg S+	↓ analgesic need, postop day 1, 2 ↓ pain at rest, postop day 1, 2	NS	small-dose S+, started before first opiate, continued in PCA
Argiriadou et al.[16] 2004	5	15/15/15 C/pre/rep	major pelvic visceral surgery / GA + intra- and postop EA with LA	S+, iv: 0.5 mg/kg preincisional + placebo, or + 0.2 mg/kg repeated intraop	repeated S+: ↓ pain over 6 h postop ↓ analgesic need, postop day 1 ↑ postop patient mood	NS	↑postop analgesia despite postop EA
Ilkjaer et al.[17] 1998	5	30/30 C/pre	renal surgery / GA + intra- and postop EA with LA for 24 h, then opiate for 48 h	racemic, iv: 10 mg preincisional + 10 mg/h for 48 h	NS	↑feeling of sedation, postop day 1	effects overshadowed by postop EA
Dahl et al.[18] 2000	5	33/33/33 C/pre/post	abdominal hysterectomy / GA	racemic, iv: 0.4 mg/kg preincisional or after skin closure	NS	NS	one injection before incision, ineffective

Weiskopf Anesthesiology. 2005.

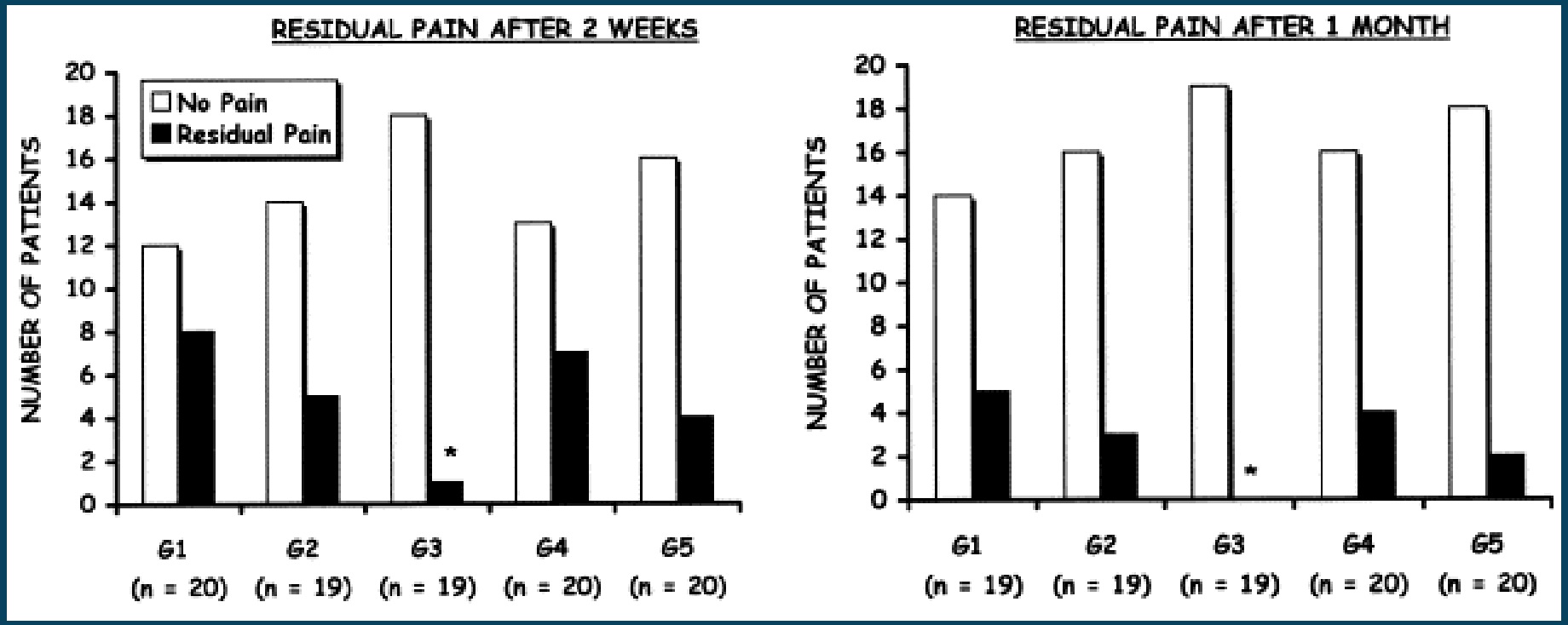
Ketamine in the OR



M. De Kock Pain 2001.

Group 1 No ketamine
Group 2 low ketamine IV
Group 3 High ketamine IV
Group 4 Low ketamine epidural
Group 5 High ketamine epidural

Ketamine in the OR



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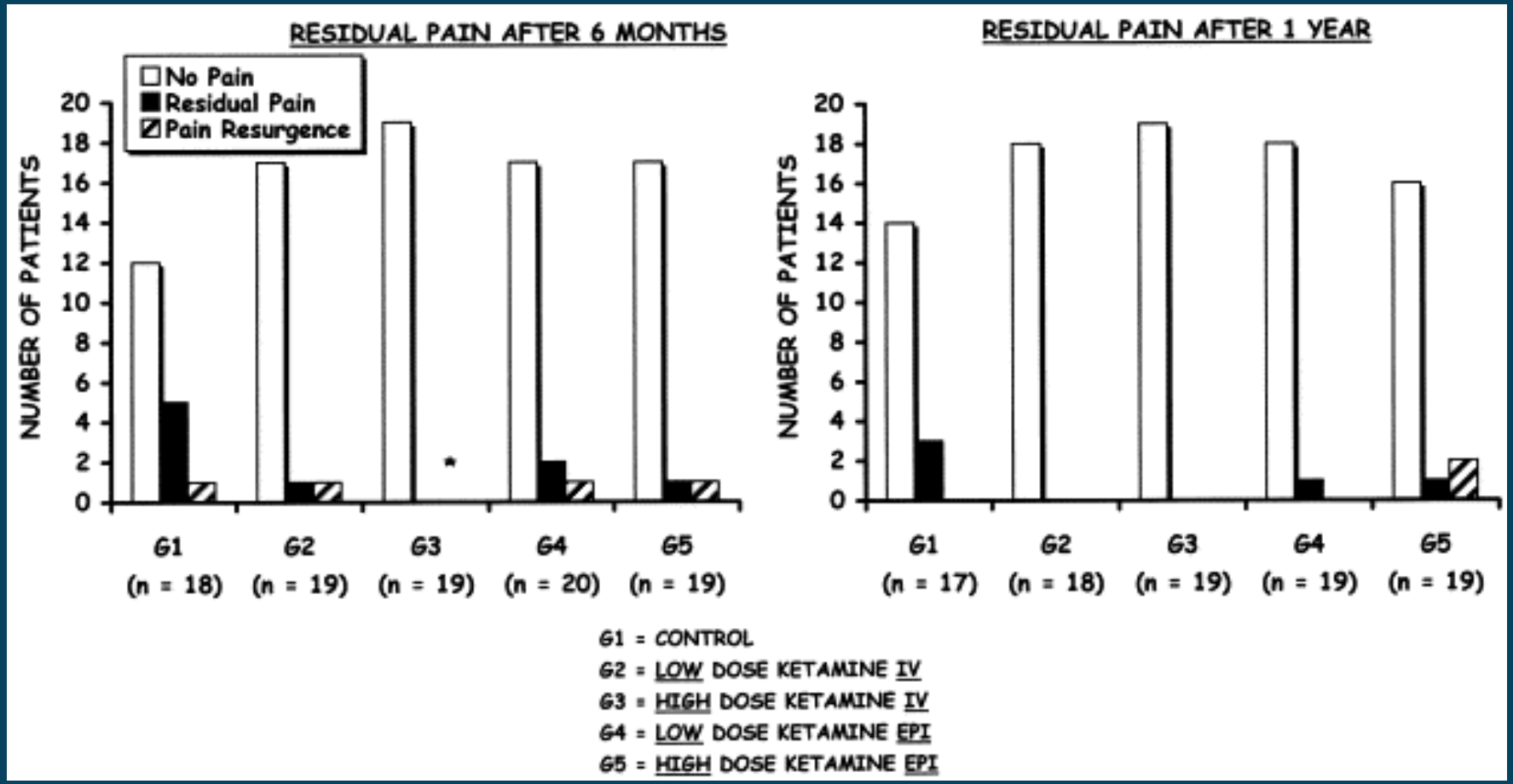

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Group 5 High ketamine epidural

M. De Kock Pain 2001.

Ketamine in the OR

The Cochrane Database of systemic reviews analyzed 27 trials involving 2240 participants and report.

- “Ketamine in subanesthetic doses is effective in reducing morphine requirements in the first 24 hours after surgery.”
- “Ketamine also reduces postoperative nausea and vomiting.”
- “Adverse effects are mild or absent.”

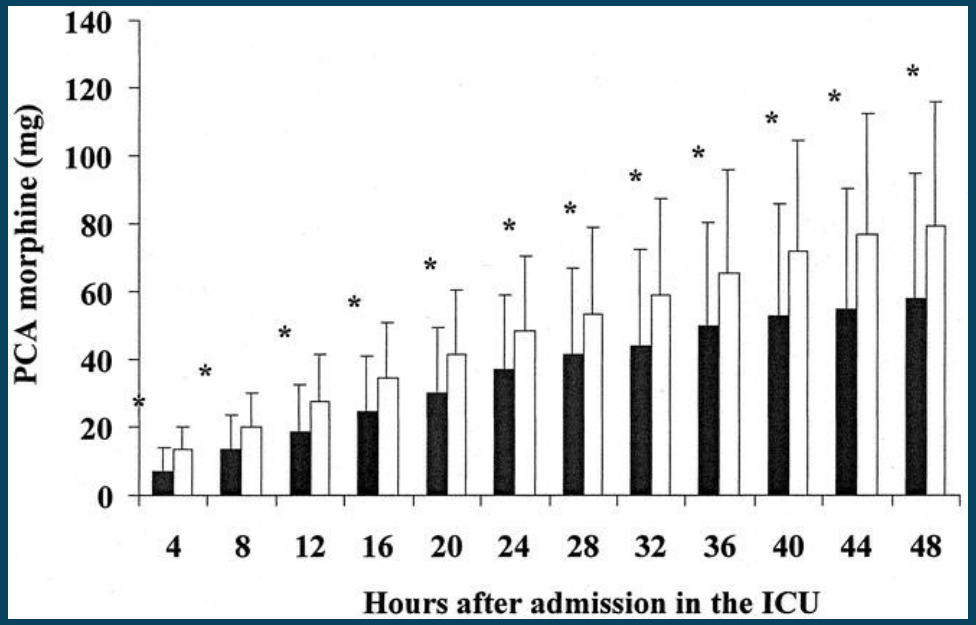
Ketamine Post Op

Subanesthetic Ketamine in the setting of PCA or infusion.

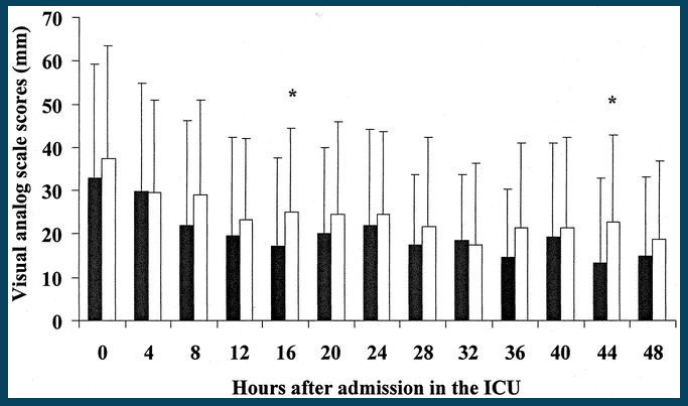
Reference	Quality Score	Size / Study Group	Study Setting / Anesthesia, Analgesia	Ketamine, Administration Schedule	Difference in Outcome Measures after Ketamine	Difference in Side Effects after Ketamine	Comment
Remifentanil-Related Opioid Phenomenon							
Guignard et al.[45] 2002	5	25/25 C/preop	colorectal surgery / remifentanil-based GA, desflurane at 0.5 MAC and remifentanil started at 15 µg/kg/h	racemic, iv: 0.15 mg/kg + 120 µg/kg/h until skin closure	↓ intraop remifentanil need ↑ time to first analgesic request ↓ analgesic need over 24 h postop	NS	small dose, started before remifentanil infusion began
Jaksch et al.[46] 2002	5	15/15 C/pre	arthroscopic knee ligament repair / GA, TCI with propofol (target 2 - 4 µg/ml) and remifentanil (7.5 - 60 µg/kg/h)	S+, iv: 0.5 mg/kg + 120 µg/kg/h until 2 h after emergence	NS	NS	S+, started after remifentanil infusion began
Postoperative Opioid-Resistant Pain							
Weinbroum[46] 2003	4	114/131 C/add	major surgery / GA / when postop pain after at least 100 µg/kg morphine in 30 min still 6 ≥ (10-point VAS), start of study	racemic, iv: 250 µg/kg + 15 µg/kg morphine, versus 30 µg/kg mophine, alone, up to 3 times in 10 min, until pain ≤ 4	after first study drug injection: ↓ pain at 10 and 120 min ↓ number of injections necessary for pain ≤ 4 at 10 and 120 min ↑ feeling of well-being at 120 min	↑ wakefulness and oxygen saturation at 10 min in PACU: ↓ nausea / vomiting ↑ sensation of light-headedness	rapid, sustained more than additive effect after combined Ket / morphine
Postoperative Patient-Controlled Analgesia							
Guillou et al.[50] 2003	5	47/54 C/add	major abdominal surgery / GA / PCA with morphine, 1 mg bolus	racemic, iv PCA: in addition 0.5 mg/kg bolus + 120 µg/kg/h for 24 h, then + 60 µg/kg/h for 24 h	↓ analgesic need over 48 h postop ↓ pain at rest at 16 and 44 h postop ↓ pain on mobilization at 16, 20, and 40 h postop	NS	in SICU: ↑ analgesia with low-dose background Ket infusion
Chia et al.[52] 1998	5	46/45 C/add	major surgery / GA / epi-PCA with morphine, 0.05 mg bolus, 2 mg Bupi, and 10 µg epinephrine	racemic, epi-PCA: in addition 1 mg bolus	↓ pain during cough / on movement postop day 1, 2, 3 ↓ pain at rest postop day 1, 2 ↓ analgesic need, postop day 1, 2	NS	↑ analgesia in multimodal epidural PCA regime
Burstal et al.[53] 2001	4	33/37 C/add	abdominal hysterectomy / GA / PCA with morphine, 1 mg blous	racemic, iv PCA: in addition 2 mg bolus	↓ time period to require PCA	↑ side effects: 4 pts with dysphoria, 4 pts with pruritus	more Ket-treated pts. withdrawn because of side effects
Unlugenc et al.[54] 2003	4	30/30/30 C/Mg/add	major abdominal surgery / GA / PCA with morphine, 0.875 mg bolus	racemic, iv PCA: in addition 0.0125 mg bolus, or Mg, 30 mg bolus	minor effect after Ket and Mg, ↓ pain and discomfort at 15, 30, 60 min postop: ↓ analgesic need over 12 and 24 h postop	NS	too small Ket dose, below effectiveness for analgesic effect

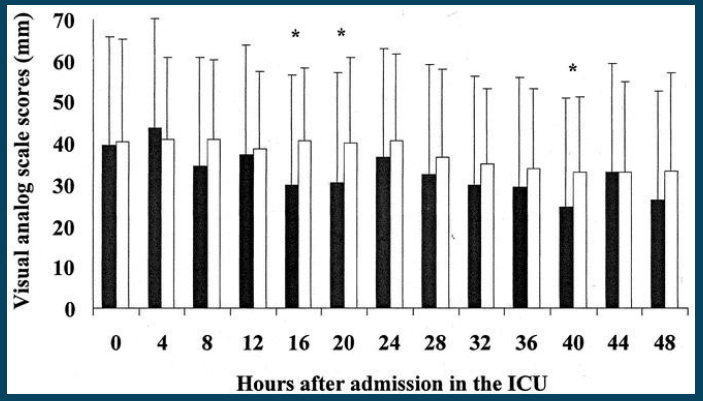
Weiskopf Anesthesiology. 2005.

Ketamine Post Op



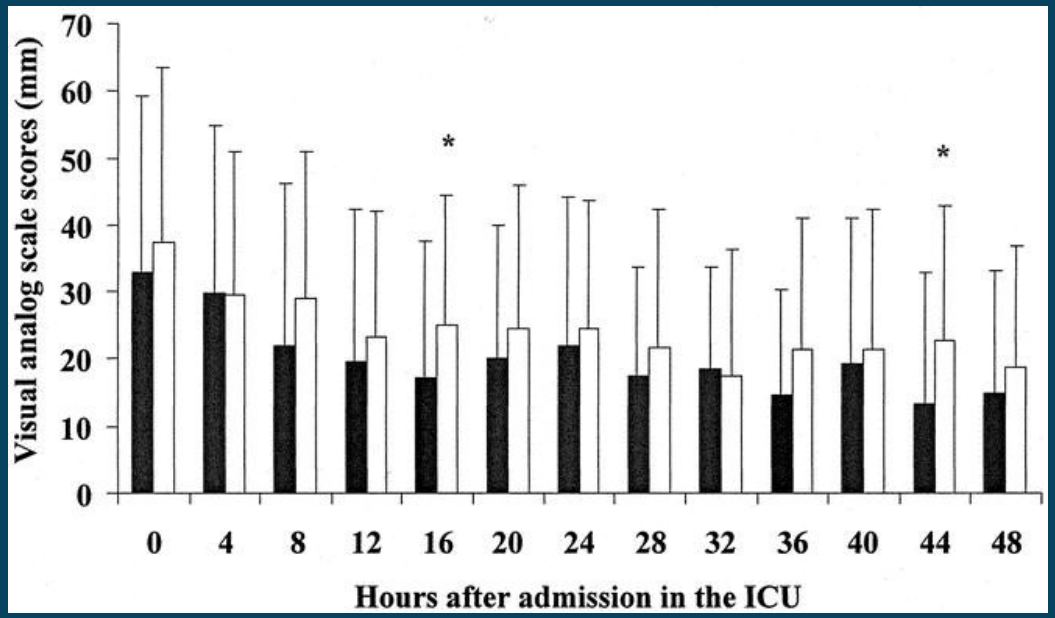
Black Bars – morphine PCA + ketamine White Bars – morphine PCA

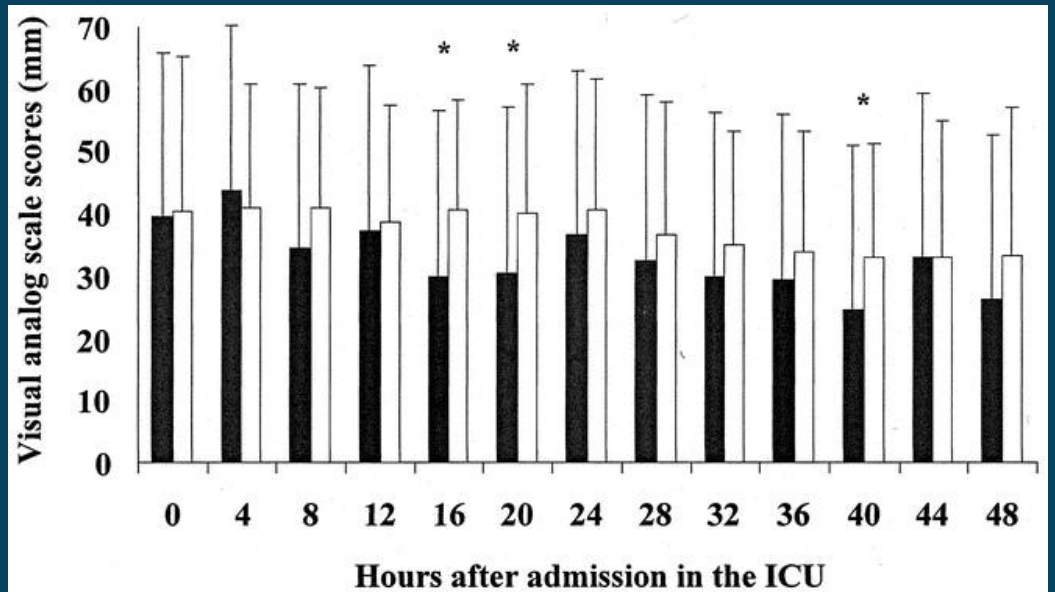




Guillou et al. Anesth Analg, 2003.

Ketamine Post Op





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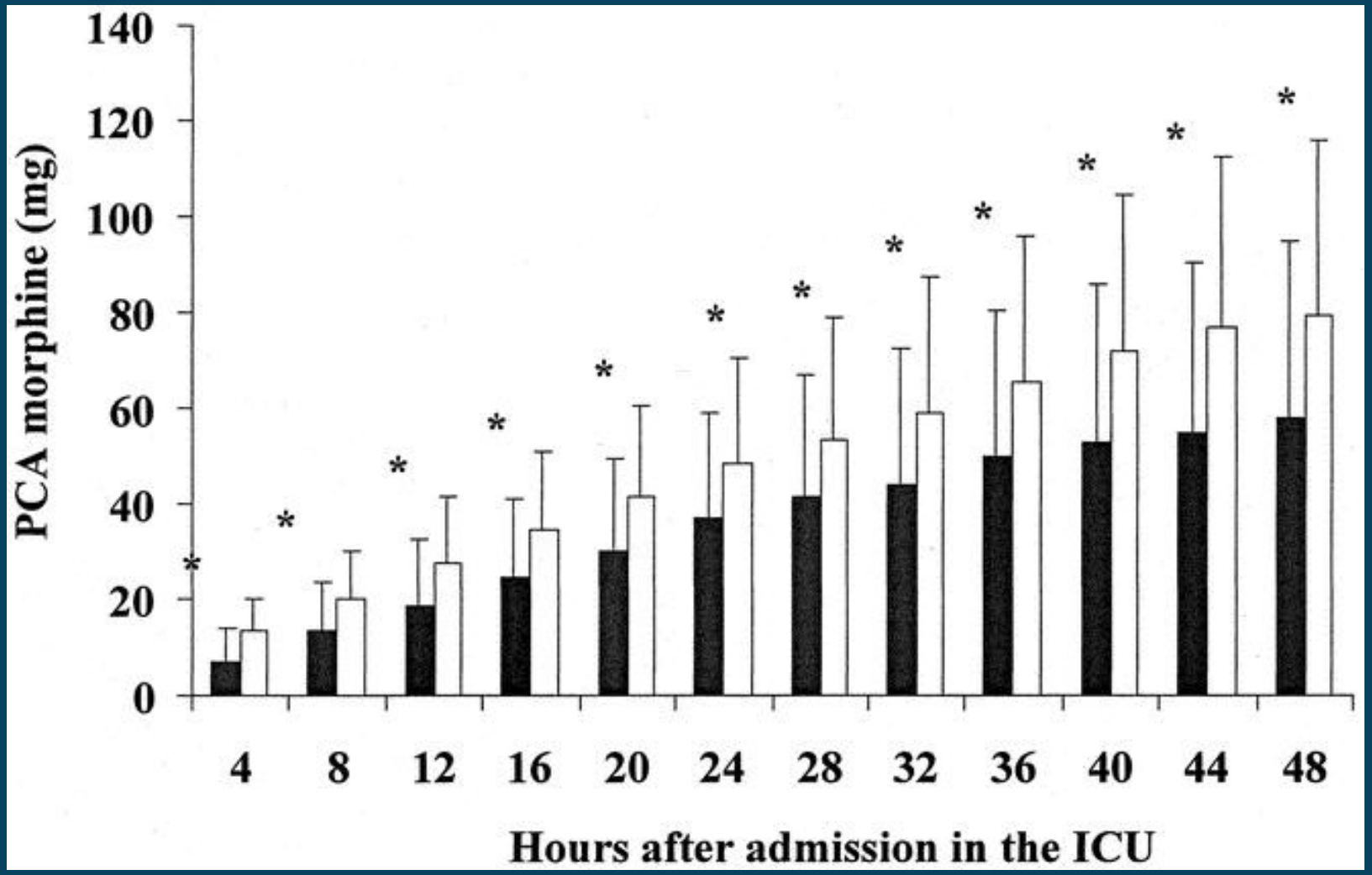
Guillou et al. Anesth Analg, 2003.

Ketamine Post Op



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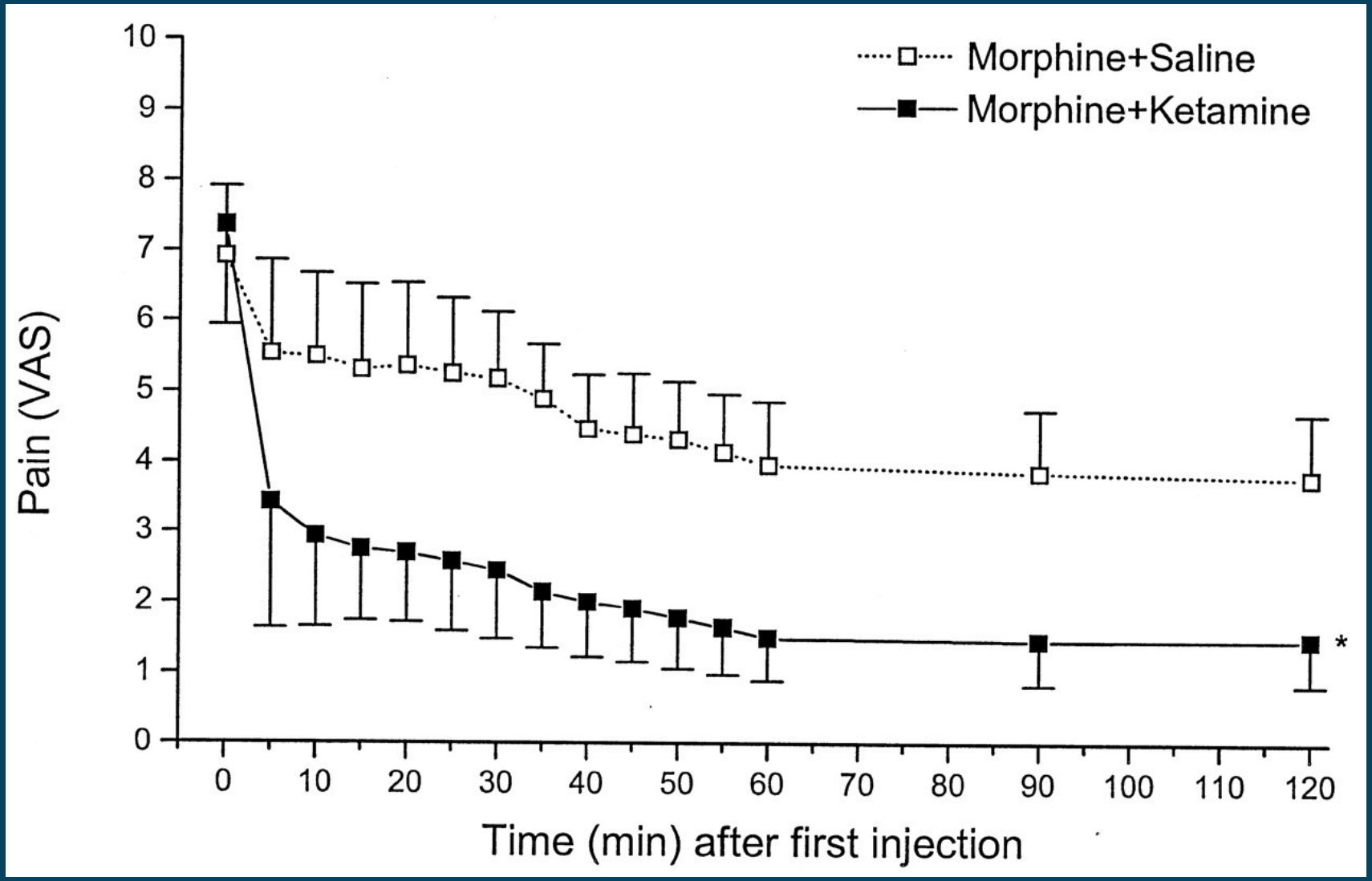
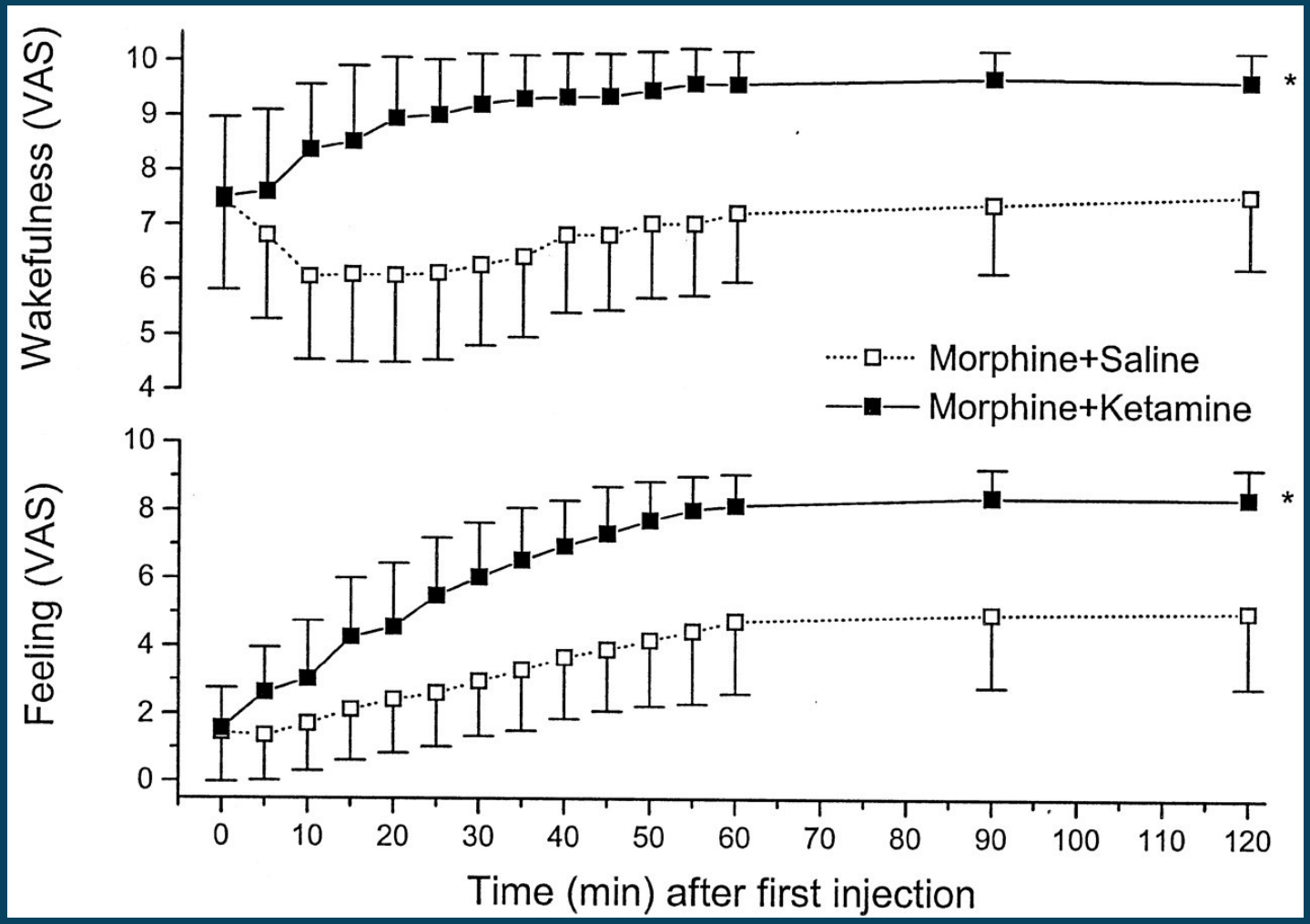


Weinbroum. Anesth Analg 2003.

Ketamine Post Op



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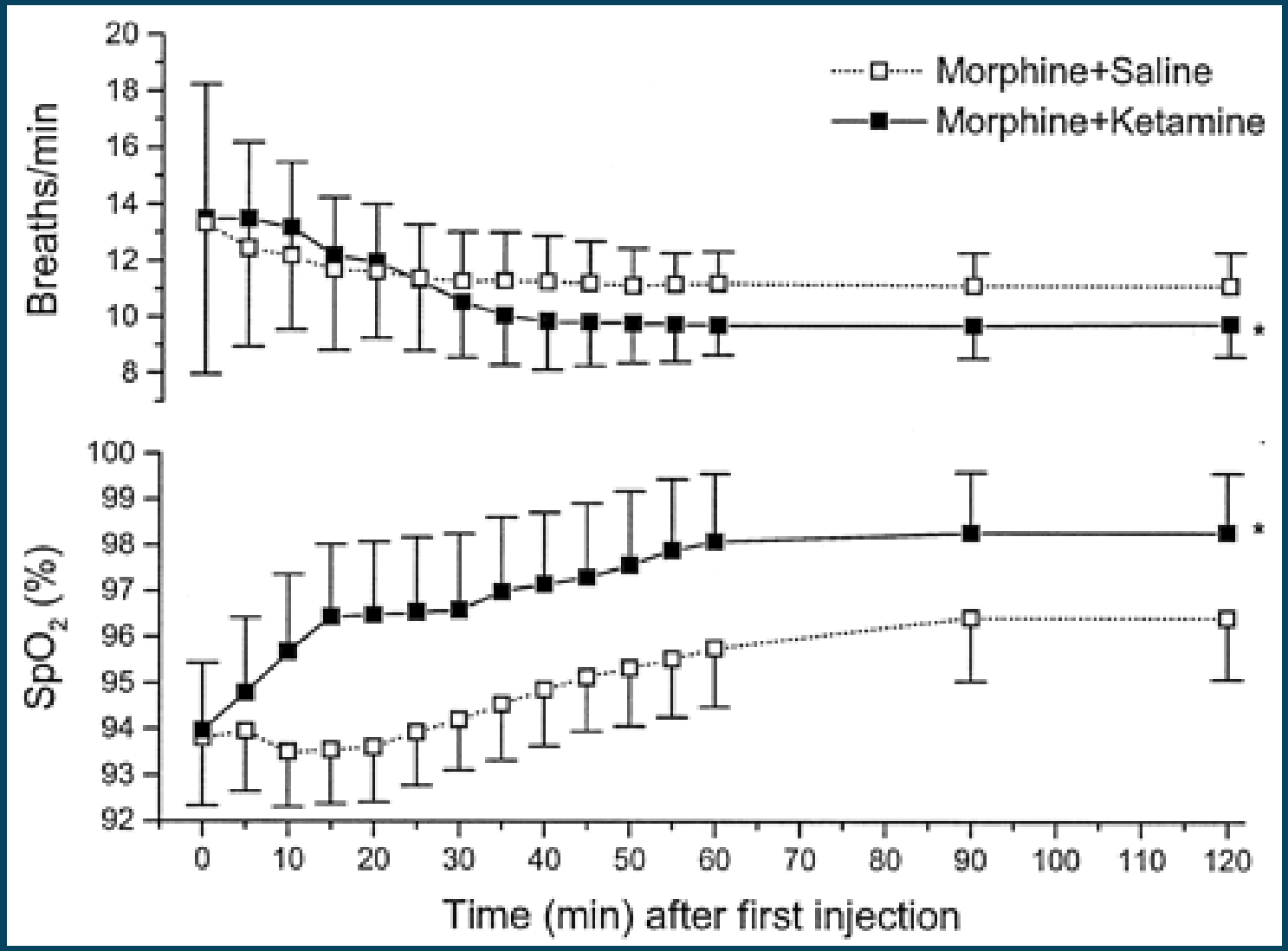

Weinbroum. Anesth Analg 2003.

Ketamine Side Effects

Variable	Ketamine group (n = 41)	Morphine group (n = 52)
Nausea	2	4
Confusion	2	2
Hallucinations	1	1
Hypoventilation	1	3
Pruritus	1	1

Weiskopf Anesthesiology 2005.

- In the setting of post operative PCA, most trails did not find a difference in adverse psychomimetic effects.
- Effects are dose dependent and less likely with small doses (<0.15 mg/kg).
- When used as an infusion at less than 10 mg/hr, cognitive impairment is negligible.
- The prophylactic use of a sedative has generally decreased the severity or mind altering effects.

Further Considerations

- Does opioid rotation decrease opioid hyperalgesia and/or tolerance?
- Do “analgesic gaps” increase opioid hyperalgesia and/or tolerance?
- Are some opioids because of different receptor or activity profiles more or less likely to induce OIH? Methadone?
- Is there a subpopulation at increased risk for OIH?
- Can other medications decrease hyperalgesia? COX IIs?
- What is the interaction between regional anesthesia and hyperalgesia?
- What is the role of supraspinal pro and antinociceptive systems?

Case Presentation Reconsidered

- “Difficult to control pain in prior admission” - particularly susceptibility to OIH.
- Long term high dose opioids – higher nociceptive/antinociceptive set point leads to rapid development or progressive hyperalgesia.
- Hydromorphone allergy precludes opioid rotation. Did well w/fentanyl rescue in the past.
- Did relatively high intraoperative opioid use enhance his eventual hyperalgesia.
- Probable analgesic gap POD#0.

Case Presentation Reconsidered

- More flexible regional technique – safer to achieve “surgical block”.
- Ketamine intraop.
- Early use of adjuncts – gabapentin, cox-2, benzodiazepenes.
- Ketamine post-op infusion v. PCA additive v. rescue.
- Opioid rotation ie methadone on POD#0.

Conclusions

- Opioid Induced Hyperalgesia is a phenomenon where treatment with opioids leads to increased sensitivity to pain.
- This increased sensitivity is present during and after treatment with opioids and appears to increase with both duration of treatment and opioid dosage.
- OIH can recur with repeat exposure to opioids or opioid antagonists.
- OIH can be induced through long term opioid therapy or through short term intraoperative use.
- NMDA receptor antagonism prevents OIH and preserves effectiveness of opioids in an animal model.
- Ketamine in subanesthetic doses intraoperatively and postoperatively can improve pain scores, decrease opioid requirement and possibly prevent development of chronic pain.
- Ketamine can be successful in rescuing patients who have failed to obtain analgesia with opioids.